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AN INTRODUCTION TO PHARMACOLOGY AND THERAPEUTICS

J. A. GUNN

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AN INTRODUCTION TO PHARMACOLOGY AND THERAPEUTICS

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BY

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'Were angels to write books, they would never write folios.'

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PREFACE

During the years in which I have had the privilege of teaching medical students in Oxford, I have given a course of lectures dealing with the actions and uses of drugs, supplemented by practical courses in Pharmacology and in Pharmacy. Owing to the increasing demands upon the medical curriculum, this yearly course of lectures has been limited to fifty. Such a course could not give much more than a general sketch of the subject, the student being left to fill in details from text-books or other sources. Without such a general survey the student is apt to lose himself in a mass of detail and often fails to get any sense of proportion or scheme of classification.

I have often wished to alter this procedure by providing the student with such a short but comprehensive survey in book form as would leave the lecturer more freedom and latitude to deal with more advanced and advancing aspects of the subject. The smaller books that are available do not furnish the desired survey because they achieve brevity by compression rather than by selection and arrangement. I am also frequently asked to recommend a book which a student can read in the vacation before attending lectures, and for this a large text-book is unsuitable.

It is for these purposes that this little book has been written, though I can hardly hope that its sphere of usefulness will be commensurate with the time I have spent upon its compilation.

J. A. G.

CONTENTS AND CLASSIFICATION

I. INTRODUCTION 1

Origin and sources of drugs. Methods of action and conditions influencing these. Methods by which drugs are administered. Preparations of drugs.

II. WATER AND SALTS 17

Normal saline solutions. Saline diuretics. Saline purgatives.

III. KATIONS OF THE BLOOD . . . 27

Sodium, potassium, calcium, ammonium.
Acids and Alkalis.

IV. DRUGS ACTING ON THE ALIMENTARY CANAL 36

Bitters. Carminatives. Purgatives. Vegetable astringents.

V. HEAVY METALS 48

Copper, zinc, aluminium, silver, lead, mercury, iron.

VI. METALLOIDS 65

Bismuth, antimony, arsenic, phosphorus.

VII. DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM 75

I. *Stimulants.*
Caffeine. Strychnine.

VIII. DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM (*contd.*) . . . 83

II. *Depressants.*
Alcohol and the general anaesthetics.

IX. DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM (*contd.*) . . . 100

II. *Depressants* (*contd.*)
Hypnotics.

X. DRUGS ACTING ON THE SENSORY NERVE-ENDS 111

I. *Stimulants.*
Counter-irritants.

II. *Depressants.*
Local anaesthetics.

CONTENTS

XI. DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM 127

A. Parasympathetic Nerves.

I. *Stimulants.*

Pilocarpine. Physostigmine.

II. *Depressants.*

Atropine. Hyoscine. Homatropine.

XII. DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM (*contd.*) . . . 139

B. Sympathetic Nerves.

I. *Stimulants.*

Adrenaline. Tyramine. Ephedrine. Ergotoxine.

XIII. DRUGS ACTING DIRECTLY ON INVOLUNTARY MUSCLE 146

I. *Stimulants.*

Barium, Pituitary, Histamine.

II. *Depressants.*

Nitrites.

XIV. DRUGS ACTING ON HEART MUSCLE . 153

Cardiac tonics.

Digitalis. Strophanthus. Squill.

XV. DRUGS WHICH INFLUENCE METABOLISM 161

Thyroid. Parathyroid. Iodides. Cinchophen. Colchicum. Vitamins. Insulin.

XVI. PHENOL AND ALLIED AROMATIC COMPOUNDS 171

Benzol. Phenol. Cresols. Volatile oils. Stearoptenes.

XVII. CENTRAL ANTIPYRETICS AND ANALGESICS 180

Salicylates. Phenacetin. Phenazonum.

XVIII. DRUGS USED IN BACTERIAL INFECTIONS . 189

Antiseptics. Antitoxins.

XIX. DRUGS USED IN TRYPANOSOMIASIS AND PROTOZOAL INFECTIONS . . . 201

XX. DRUGS USED IN WORM INFECTIONS . 209

Anthelmintics.

INDEX 214

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INTRODUCTION

I. Origin and Sources of Drugs

All races of mankind have tried to heal those who suffer from diseases, and of the many curative methods which have been employed, one of the most ancient and successful has been treatment by means of drugs. The drugs which are used medicinally at the present day have been discovered at different times and in different countries. They come from different sources; animal, vegetable, and mineral substances, as well as artificially prepared compounds, have all been pressed into service as remedial agents.

It is not difficult to imagine how, for example, plants came to be used as remedies. Man had to discover which plants were edible and which were not. They bore no labels. In the process of seeking for food, it would be found that some plants produce unusual effects. They might purge, for example, and the step would be a fairly easy one to use such a plant as a remedy for constipation. Some would be found to be powerful poisons, and extracts of these came to be used in some countries, for example, as arrow poisons. Long before there was any science of experimental pharmacology, or even before there was any real knowledge of the causes of disease, a large amount of information had thus accrued of the remedial and toxic properties of plants.

One can imagine also how an elementary knowledge of pharmaceutical processes would arise. A recognition of any unusual action of a plant might result at first from eating a leaf. A leaf stored for future use might crumble, and it would be found that the leaf

retained its activity in the form of a powder. If it were cooked, it might be noticed that the active properties of the plant were conveyed to the water in which the plant was cooked, and even to the residue left when the water evaporated. So might come about the employment of plants in the form of a powder, an infusion, or an extract, methods of preparation which are still in use.

It required a much greater knowledge (in some cases a very modern knowledge) of chemistry to determine what particular constituent of a plant was responsible for its curative or toxic actions, and to determine the chemical nature of this, the active principle as it is called. This kind of knowledge has really been acquired only in the last century. For example, cinchona bark was used as a remedy for malaria for about two centuries before the active principle, quinine, was isolated from it. The active principles of most important medicinal plants are now known, and in some cases their exact chemical composition. Especially in the last fifty years it has become possible with advancing knowledge to use the active principles in place of a crude drug or of extracts from it. The amount of active principle in a plant varies with such factors as the soil in which it grows and the climate. Even if an extract is always made in the same way, therefore, its activity will vary. But the active principle is a definite chemical substance, of unvarying composition and often more stable than an extract, and therefore dosage with it can be more accurate.

One large group of drugs, therefore, consists of plants or parts of them, of extracts made from plants, and of active principles—alkaloids for example—isolated from plants. Other substances have been used as remedies. Some of these are substances occurring in nature like sulphur, compounds of iron, or salts like

Epsom salts. A very important group of drugs has been introduced especially in the last half-century or so, substances which have been manufactured in the chemical laboratory. An early type of such a substance would be alcohol, manufactured by the fermentation of sugar. The important anaesthetics chloroform and ether are artificially made, so are most of the hypnotics. chloral and veronal for example.

Though plant constituents continue to be investigated with a view to discovering new remedies, an increasing number of new drugs are compounds artificially synthesized or manufactured in the chemical laboratory.

It follows from this that not only have drugs come to us from different sources and through different channels, but our knowledge of their action and effects has been variously acquired. Drugs were employed in the treatment of diseases long before the pathology of these diseases was understood. The investigation of the physiological actions of drugs is a comparatively new science. In the course of time, therefore, various remedial actions of drugs were discovered for which no scientific explanation could, at the time, be given. With the advances in knowledge of physiology, pathology, and pharmacology, especially in the last half century, these explanations have in many cases been forthcoming. To make a rough classification, our present knowledge of the effects of drugs has been acquired in two ways. Older remedies were discovered chiefly by observing their remedial effects in diseases in man, while the pharmacological basis of these effects has only recently, and as yet imperfectly, been established. On the other hand, substances, artificial or other, which are now for the first time investigated as to their possible value as remedial agents, are first examined, usually on laboratory animals, as to their physiological actions and toxicity, and it is upon the

results of this investigation that a possible field for their tentative therapeutic use is based.

This kind of experimental investigation, which is really a branch of physiology, is called *Pharmacology* (Greek, *pharmakon*, a drug), which may be defined as the action of drugs on normal animals or tissues. *Therapeutics* (Greek, *therapeuein*, to heal) is, in this connexion, the application of this knowledge to the treatment of disease.

The term *Pharmacognosy* is applied to the knowledge of the sources and chemical properties of drugs, while the art of preparing drugs in forms suitable for medicinal administration is called *Pharmacy*.

As a guide to the physician and pharmacist, most countries publish from time to time an authoritative list of drugs in general use with certain information regarding them. This book gives an account of the sources and physico-chemical properties of drugs, with their doses, &c. It contains also a description of standard 'preparations' of drugs. As new drugs are introduced or old ones discarded, this list has to be revised. In this country the book in question is called the *British Pharmacopoeia* and is published under the authority of the General Medical Council, a new edition being necessary every ten years or so. Drugs or preparations which receive recognition in this book are called 'official' or pharmacopoeial remedies; or the initials (B.P.) are placed after the name of the drug. Similarly (U.S.P.) stands for the Pharmacopoeia of the United States.

II. Methods of Action of Drugs and Conditions Influencing These

Local and general actions.

By **local action** is meant the action which a drug exerts at the site of application and before it is ab-

sorbed into the blood-stream. This includes not only such obviously external actions as for example the action of an ointment on the skin or of a solution applied to the conjunctiva, but also the action of a gargle on the surface of the throat or of a solution used to wash out the bladder. As in the majority of cases drugs are administered by mouth, they have then the opportunity of acting first on the surface of the alimentary canal, effects which are included among local actions.

By **general action** is meant the action of a drug *after absorption*. In this case the drug is carried by the blood to all the tissues in the body, which therefore are all subjected to the same concentration of it. It is found, however, that under these circumstances the different tissues of the body are not equally sensitive to the action of any drug. In other words, drugs have what is called a *selective action* on the tissues. This selective action is more marked with some drugs than with others, but is displayed by them all. Indeed the possibility of their being used medicinally depends upon this. When a dose of 2 milligrammes of strychnine is given intravenously to a man weighing 70 kilogrammes, the concentration in the blood (once it is evenly distributed and before any of it is excreted) is about 1 part in 2 or 3 millions. This concentration may stimulate the central nervous system, but even much larger doses, which would give correspondingly higher concentrations in the blood, have no such effect on other tissues. Extract of pituitary gland is extensively used to stimulate the contractions of the uterus in labour, but it could hardly be used for this purpose if it had an equal effect on the muscle of the bronchi, because in this case an undesirable attack of asthma would accompany the desired action on the uterus. It will be readily understood that one generally desires a drug to act only on one organ or system, and

it is upon the fact that they usually do this—that they exhibit a selective action on particular organs—that the therapeutic use of drugs depends.

When strychnine acts on the central nervous system or pituitary extract on the uterine muscle, it may be presumed that there is some physical or chemical reaction between the drug and the tissue acted upon. As to the nature of such reactions we have scarcely any accurate knowledge. When one considers the complexity of the chemical structure of living cells and the fact that the chemical constitution of strychnine or of the active principle of pituitary is still unknown, the fact that we cannot as yet explain the *interactions between living cell and drug* is not surprising. In the case of drugs of simpler constitution producing grosser actions, a chemical explanation can in some cases be given; for example, the caustic action of silver nitrate is due in part at least to the precipitation of the proteins of the cell by the silver ion.

Though our knowledge of the reactions between cell and drug is as yet meagre, it has been found that substances of similar chemical constitution often produce similar pharmacological actions. When the structural composition of adrenaline was once determined, not only could adrenaline be manufactured synthetically in the laboratory, but other natural and artificial compounds having a similar chemical composition were found in many cases to exert physiological actions more or less similar to those produced by adrenaline. Though this kind of investigation into what is called the *relation between chemical composition and pharmacological action* has not achieved all that was originally hoped for it, it has greatly increased pharmacological knowledge and added new and useful drugs.

When strychnine acts on the central nervous system, or in general when any drug acts on any organ,

it cannot alter the normal functions of that organ. No drug can, for example, cause a nerve-cell to contract rhythmically, or a cardiac cell to exhibit reflex action, or a salivary gland to secrete bile. All a drug can do is to increase or decrease the excitability of a nerve-cell, make the heart go slower or faster, or make a salivary gland eliminate more or less of its normal secretion. In other words, *drugs can only change activities of organs quantitatively, not qualitatively*; but this quantitative change, combined with the selective action of drugs, is fortunately usually enough for our purpose. The fact that a drug can only increase or decrease the activities of an organ, and that it will obviously make all the difference in which of the two ways it acts, necessitates the continual description of pharmacological action as *stimulation or depression* of the activities of organs; but from what has been said it will be clear that from this reiteration there is no escape.

Two milligrammes of strychnine injected into a man may produce a just measurable increase in the excitability of certain reflexes; two grammes will cause death immediately from violent convulsions. A small (therapeutic) dose of atropine may stimulate certain parts of the central nervous system, which will be paralysed by a larger dose of the same drug. Very weak concentrations of quinine may accelerate the movements of amoebae whereas higher concentrations will arrest those movements. It is clear, therefore, that one cannot speak of the actions of a drug as something fixed. The degree of action always, and even sometimes the type of action, depend upon the dose or concentration. When digitalis is given, it may have no effect, slow the heart, quicken the heart, or arrest the heart for ever, according to the dose that is given. Seeing, therefore, that whenever a drug is intelligently prescribed it must be given with the intention

of producing a definite effect, it would seem to be obvious that the question of **dosage** is all-important. And yet much of the doubt and confusion that still prevails regarding the pharmacological actions and therapeutic values of drugs is due to want of persistent recognition of this elementary fact. To the student beginning this subject, the task of learning doses is bound to be wearisome, but it may be some consolation to remember that the remedial value of every single drug depends entirely upon the dose of it that is given. For the guidance of the practitioner a pharmacopoeia, therefore, mentions the doses of drugs; the British Pharmacopoeia gives a minimum and maximum dose, whereas the United States Pharmacopoeia gives only an average dose.[1] This official dose means a single dose that is generally suitable for an adult man, and in many cases it is a dose that can be repeated two or three times in a day. It will perhaps not be difficult to understand that no general rule can be given for the total amount of different drugs that can be given with advantage over longer periods, as this will depend upon so many varying factors.

There are certain **conditions influencing dosage** which may be conveniently mentioned here. When a drug is given, for example, to produce some action after

[1] WEIGHTS AND MEASURES

In both British and U.S. Pharmacopoeias doses are given in the Metric System with approximate equivalents in the Imperial System. In this book doses are given in the Imperial System only, as this is still in more general use.

According to Apothecaries' Weights, which are chiefly used in *retail* dispensing:

60 grains = 1 drachm
8 drachms = 1 ounce (= 480 grains).

The measures of volume are:

60 minims = 1 fluid drachm
8 fluid drachms = 1 fluid ounce (= 480 minims).

For converting doses in the Apothecaries' System into doses in

absorption, the amount of effect that it produces depends usually upon the concentration of the drug in the blood, and consequently upon the volume of the blood. As the volume of blood in an infant will be much less than that of an adult, a proportionately smaller dose will be required to produce the same concentration of the drug in the blood. If one regards the drug as evenly distributed through all the tissues, the general result will be the same. In animals of the same species, therefore, the dose of a drug required to produce a given effect ought to be roughly proportioned to *body-weight*; and this is found to be the case, though, with some drugs especially, it may be more nearly proportional to body-surface. In any case the dose for a child will depend upon its size and weight. It is not always convenient to weigh a child, and the estimation of the surface area of the body requires some mathematical calculation; but it is usually possible to obtain the age of the child, and as this bears some relation to size and weight, a rough estimate of dosage can be made on the basis of *age*. One simple

the Metric System, the following approximate equivalents will assist:

Weights

Imperial		*Metric*
$\frac{1}{100}$ grain	= 0·6 milligrammes	= 0·0006 gramme
$\frac{1}{10}$,,	= 6 ,,	= 0·006 ,,
1 ,,	= 6 centigrammes	= 0·06 ,,
10 ,,	= 6 decigrammes	= 0·6 ,,
15 ,,	= 10 ,,	= 1 ,,
1 drachm		= 4 ,,
1 ounce		= 30 ,,

Volumes

Imperial		*Metric*
1 minim	= 6 centimils	= 0·06 mil. or c.c.
10 ,,	= 6 decimils	= 0·6 ,,
15 ,,	=	= 1 ,,
1 fl. drachm		= 4 ,,
1 fl. ounce		= 30 ,,

formula for this, called Young's Formula, is to take the age divided by the (age plus 12), which gives a fair average fraction of the adult dose which is suitable for a child. For example, a child of three would get three-fifteenths or one-fifth of the adult dose. With these precautions a suitable dose of most drugs for most ages can be estimated.

Even with these precautions, however, and even if the dose be accurately measured in proportion to body-weight, it will still be found that individuals vary in their reaction to drugs. A marked divergence from normal reaction is called *Idiosyncrasy*, which merely means any kind of peculiar reaction. An individual may show an excessive reaction to a normal dose (*Hypersusceptibility*), for example infants are hypersusceptible to opium: or a diminished reaction (*Tolerance*), for example children are very tolerant of mercury: or an unusual reaction (Idiosyncrasy proper), for example a usual dose of quinine produces in a small proportion of people a severe nettle-rash. Though these divergences are of sufficient importance to merit attention in dealing with individuals of the same species, they are much more conspicuous in members of different species. For example, in regard to digitalis, the toad (weight for weight) will withstand enormous doses as compared with the frog, or the rat as compared with the rabbit.

Tolerance may be of two kinds. It may be inborn, in which case it is usually called *Natural Tolerance*; or it may be attained through repeated administration, in which case it is called *Acquired Tolerance*. The latter kind of tolerance is especially prone to occur with hypnotic drugs; a person, for example, who habitually indulges in morphine may come to withstand a dose which would kill several people who were unaccustomed to it. It is important to remember that acquired

tolerance to drugs is usually, if not always, of a different nature to acquired immunity to proteins, toxins, or bacteria. In the latter case repeated administration induces the tissue-cells to manufacture and shed off into the body-fluids antibodies which neutralize or inactivate the foreign substance. Tolerance to drugs, however, is acquired in other ways; usually the body acquires an increased power of oxidizing or of excreting the drug, or the cells become, in some way not yet understood, more resistant to its action.

III. Methods by which Drugs are Administered

Before considering the action of drugs in detail, it may be well first to consider the chief methods by which drugs are administered, though some of these, being matters of common knowledge, will be already familiar. Naturally, one of the commonest methods of giving drugs is *by mouth*. This is the obvious method of administration when an action is desired on the alimentary canal, but drugs can also be given by this channel with a view to their absorption. Drugs vary very much in the readiness with which they are absorbed from the alimentary canal. With the important exception of alcohol, few drugs are absorbed from the stomach; absorption occurs chiefly from the small intestine and occurs there in all degrees, ranging from the swift absorption of iodides to the almost complete inabsorbability of liquid paraffin. A frequent drawback to oral administration is that drugs may be chemically altered in the alimentary canal, or they may interfere with digestion. Drugs may also be given *by rectum*, either for a local action on the lower bowel or with a view to absorption.

Either to avoid chemical change or merely for speed of action, drugs may be injected under the skin. As

many substances, especially if soluble in the body-fluids, are absorbed more rapidly from *hypodermic injection* than from the intestine, while the rate of excretion is uninfluenced, the concentration of the drug in the blood is, as a general rule, temporarily higher with subcutaneous injection than with oral administration. The dose necessary to produce a given effect is therefore usually smaller; it varies in the case of different drugs, but is often about one half. If a drug is likely to cause much pain if injected under the skin, it can be injected into a muscle instead. From such an *intramuscular injection*, drugs are, as a rule, more rapidly absorbed than from hypodermic injection, for the muscle is more vascular than the subcutaneous tissues. When it is imperative that a drug should enter the blood-stream unaltered or immediately, it may be given by *intravenous injection*. Injected into a vein, a drug exerts its full action often instantaneously, while the time afforded for excretion, as compared with the time of entering the blood, is negligible. The dose is usually correspondingly small and must be very accurate, and usually the drug should be injected slowly and well diluted.

IV. Preparations of Drugs

As one might anticipate, for these different methods of administration drugs have to be prepared in different ways. In a medical 'prescription' the physician gives written directions to the dispensing chemist as to how a drug or combination of drugs is to be prepared for administration in a particular case. Often such a prescription may be very simple. For example, a drug, such as aspirin, which has a definite chemical composition and can be obtained pure, which has little taste and is given in a dose that can conveniently be weighed, may be prescribed as such—as a powder—in the

requisite quantities. On the other hand, other drugs, especially parts of plants, may have to undergo a series of manipulations before they are in a condition suitable for administration. For example, digitalis (foxglove) leaf can be used simply as the dried powdered leaf which can be prescribed as a powder in the same way as aspirin. But for some purposes it is more convenient to prescribe a solution of the active principles of the leaf, which will get rid of many constituents of the leaf which have no desirable physiological action. As the active principles in question are soluble in alcohol, such a solution (a tincture) can be made by percolating the leaf with alcohol. The amount of active principles in such a tincture (upon which its pharmacological activity and dose will depend) will vary with such factors as the degree to which the leaf is powdered, the strength of the alcohol used, the time of percolation, &c. As the activity of the resulting tincture will thus depend upon so many varying factors and its preparation requires many hours and can only be economically done with a large bulk of material, it would be an obvious advantage if, instead of every physician prescribing a tincture of digitalis according to his own formula, a standard tincture could be used which would always be of the same strength and which the dispenser could have in stock ready for immediate use. This is what is actually done, and the pharmacopoeia gives precise directions for the manufacture of such a standard tincture, which is the official 'Tinctura Digitalis'.

The pharmacopoeia includes, therefore, not only drugs themselves, but a large number of such 'Preparations'. As has already been explained, for a drug like aspirin no special preparations may be necessary; other drugs have several official preparations, e.g. opium has fifteen. At one time the medical student

was compelled to learn long lists of such preparations, with details as to their manufacture and composition. There is so much to be learnt nowadays of far greater interest and importance, that knowledge of this kind, which in any case is largely outside his sphere, is not demanded of the medical student. In this book only a selection of pharmacopoeial preparations is mentioned. In regard to these it will be impossible to explain in each case why a particular preparation has merited inclusion in the pharmacopoeia. It is important, however, to remember that the official preparations of drugs are not due to mere caprice of some authority, but are generally based upon two factors—the physical or chemical properties of a drug and the uses to which it is put. That there is an official tincture of digitalis, for example, depends upon the facts that the active principles of the leaf are soluble in alcohol, and that a tincture is a convenient form of giving digitalis which is often prescribed in mixtures. Digitalis is, however, never applied to the skin, and therefore there is no occasion, for example, for an official ointment of it. On the other hand, there is an ointment of ammoniated mercury in the pharmacopoeia, but no tincture. The reasons for this are that ammoniated mercury is never given internally and in any case will not dissolve in alcohol. It is, however, extensively used as an antiseptic for skin diseases and for this purpose can be advantageously applied as an ointment. For convenience of the physician and the dispenser, the pharmacopoeia gives instructions for making a standard ointment, i.e. Unguentum Hydrargyri Ammoniati, which is of a strength and composition generally useful, namely 5 per cent. of ammoniated mercury in benzoated lard.

The different types of official pharmaceutical preparations come under the subject of Pharmacy, but the more important may be briefly mentioned here.

As already mentioned, they depend partly upon the physical and chemical properties of the drugs, especially upon their solubilities, and can be classified in part on this basis. **Water** is frequently used as a solvent, and the resulting preparations are differently named according to the process used. A solution of a non-volatile substance is called a *Liquor*; if the substance be volatile, an *Aqua*. An *Infusum* is obtained by treating the prepared drug with (usually boiling) water and straining. A *Syrupus* consists of a strong solution of cane-sugar in water, in which a drug may be dissolved.

Alcohol is used as a solvent in Tinctures (*Tincturae*), which are prepared in various ways. If the substance is volatile, the alcoholic solution is called a spirit (*Spiritus*). In *Glycerina* B.P. (*Glycerita* U.S.P.), the solvent is a mixture of **glycerine** and water. Most of these preparations are for internal use.

Preparations can also be classified according to their method of administration. For oral administration drugs can frequently be given simply in the form of a powder (*Pulvis*). The pharmacopoeia contains several compound powders which correspond to complete prescriptions. For reasons of portability, keeping qualities, &c., solid substances may be compressed into tablets (*Tabellae*) or made into lozenges (*Trochisci*), or incorporated with some suitable excipient into the form of a pill (*Pilula*).

Substances may also be given by mouth in fluid form, generally called a mixture (*mistura*). A mixture may contain substances in solution, suspension, or emulsion. They are in this way easily swallowed, and domestic measures of volume can be used for subdivision. In routine practice, therefore, drugs are very frequently prescribed in mixtures. Usually the physician prescribes them according to his own formulae,

but the pharmacopoeia contains a few standard mixtures.

Similar fluid preparations for injection into the rectum are called *Enemata*; while solid conical bodies used for insertion into the rectum are called *Suppositoria*.

A solution used for hypodermic injection, since it usually contains only one active substance, can easily be made up as required, but the British Pharmacopoeia contains a few which are in frequent use.

For external application a drug may be incorporated with a fatty basis in an ointment (*Unguentum*); if intended to be applied with friction, it can preferably have an oily or alcoholic basis, in which case the preparation is called a liniment (*Linimentum*). A solid adhesive preparation for stationary application is called a plaster (*Emplastrum*).

Special preparations are often required for application to mucous surfaces, e.g. of the throat, eye, urethra, &c.; but these are usually made up as required, and few such preparations have as yet found their way into the pharmacopoeia. Exceptionally the British Pharmacopoeia contains a few *Lamellae*, which are thin medicated disks of gelatin and glycerine used for application to the eye.

II

WATER AND SALTS

Living protoplasm may be regarded as a liquid, containing various colloids and crystalloids in solution. It is not homogeneous, like a solution of sodium chloride, but contains an immense number of particles in the colloidal state. In order to prevent indiscriminate diffusion of substances from the protoplasm into the surrounding medium, and to maintain the identity and integrity of the cell, the latter is surrounded by a limiting membrane. This membrane is generally believed to be composed of a complex colloidal mixture of proteins and lipoids; and is impermeable to colloids but permeable to substances soluble in lipoids. The permeability to salts, sugar, and water varies with different cells or even with the same cell in different states of functional activity. Most animal cells are, however, permeable to water and some salts, and are therefore free to change their dimensions by giving up or absorbing water. In order that they may remain in a normal state, therefore, they must be surrounded by an isotonic medium, with which they keep in equilibrium. Most cells of the body may be regarded as surrounded by blood-plasma or by lymph, these body-fluids being a solution of proteins, salts, &c., in water. Unless there were some mechanism for keeping the composition and osmotic pressure of these fluids constant, the cells would be liable to continual changes in composition and in size. One of the functions of the kidneys is to maintain the constancy of these fluids in spite of the changes which would otherwise result from variations in the intake and output of water or salts. A consideration of all that is involved

in the action of water and salts would therefore comprise a considerable part of general physiology. It is possible here, however, only to deal briefly with the action of water and salts in so far as they are of practical application in therapeutics.

Though it is possible up to a point to discuss generally the action of water and salts from the point of view of their passage through a semi-permeable membrane according to the laws of osmosis, a brief consideration will show that it is not easy at present to explain all the phenomena by simple physical laws. For example, a red blood corpuscle will swell up if placed in a hypo-tonic solution. The osmotic pressure of the contents of the red cell being higher than that of the surrounding medium, water passes into the corpuscles through the membrane of the cell which is permeable to water. But all cell membranes are not similarly permeable to water. For example, water is scarcely at all absorbed from the stomach, though the osmotic pressure of contents of the cells of the mucous membrane must be higher than that of water. Similarly cells vary in their permeability to salts: for example, the cells of the intestinal mucous membrane are freely permeable to sodium or potassium, but the red blood corpuscles of the rabbit, which contain a much higher percentage of potassium and lower percentage of sodium than the surrounding plasma, must be impermeable to both potassium and sodium. Though cells thus differ in regard to their permeability to salts and water, there are certain effects produced by the latter that can be ascribed mainly if not entirely to changes in osmotic pressure which they induce in the tissues.

Water

Water does not penetrate easily through the epidermis; mucous membranes or raw surfaces are, how-

ever, more permeable. If water is applied to the conjunctiva or the nasal mucous membrane, it passes into the cells owing to the higher osmotic pressure in their interior, and the superficial cells therefore become swollen. This causes irritation or even pain, which can be avoided by using an isotonic solution. A convenient isotonic solution is *normal saline*, which consists of 0·85 per cent. sodium chloride in sterile water. For irrigating sensitive surfaces, such a solution is therefore preferable to water. Similarly a hypodermic injection will, other things being equal, cause the less irritation or pain the nearer the solution is to normal tonicity. With intravenous injections it is especially necessary that the solution injected be near the osmotic pressure of the blood. If a considerable bulk of distilled water be rapidly injected into a vein, water will pass into the corpuscles, which will swell or rupture, with discharge of haemoglobin into the plasma. For intravenous injections an isotonic solution must therefore be used.

We could hardly have reached our present stage of evolution if any such dramatic effects were to result from the ingestion of water. As we should expect, therefore, even distilled water produces no local irritation of the stomach, and only transient effects on the blood and tissues when absorbed. Water is absorbed most rapidly from the small intestine, less from the large intestine, and hardly at all from the stomach. The water absorbed brings about a dilution of the blood and a lowering of its osmotic pressure. This in turn leads to an increased filtration through the glomeruli of the kidneys with an increased secretion of watery urine and a restoration of the blood to its normal osmotic pressure. If there be an undue loss of water, e.g. by profuse sweating, the blood becomes more concentrated. This, among other effects,

diminishes the secretions of the mouth and throat and induces the sensation of thirst, which is a powerful incentive to increasing the intake of water whereby the blood is restored to its normal concentration. The mechanism for adjusting the intake and output of water is therefore usually adequate under ordinary circumstances. There are, however, some conditions which may be benefited by increasing the intake of water. The increased flow of dilute urine resulting from drinking large quantities of water is sometimes helpful in washing out the urinary passages and in allaying irritation of their surfaces.

The drinking of cold water benefits fevers by keeping the mouth clean, relieving thirst, and especially by acting as an antipyretic by facilitating perspiration and loss of heat. Drinking of water or mineral waters is also credited with beneficial effects in various diseases of metabolism such as gout or chronic rheumatism, operating in these cases presumably by facilitating the excretion of some waste products.

Salts

Physical (e.g. osmotic) effects of any importance can only be produced by soluble salts which can be given in considerable quantities. They can only be given in such quantities if neither ion possesses any pronounced physiological action. In the case of sodium cyanide, for example, the cyanide ion is so toxic that its action entirely overshadows the osmotic effects which would be produced even by a lethal dose of the salt. A dose of 5 grains of sodium cyanide may prove fatal; on the other hand, a person may consume 15 grains or more of sodium chloride with an egg. As no conspicuous osmotic effects are produced by the latter, it is evident that the osmotic effects produced by even a fatal dose of sodium cyanide will be negli-

gible. Indeed, for practical purposes, it may be taken that when a salt is given to exert a purely osmotic action of any importance, it must be given in doses of at least 15 grains.

For a consideration of mere salt action, apart from specific effects of either ion, **sodium chloride** has obvious claims to be taken as representative. It is taken in the food in amounts varying perhaps from 50 to 150 grains per day, and a corresponding amount is excreted daily in the urine. It is present in large and almost constant amounts in the blood and tissues. For practical purposes it may, therefore, be taken as an 'indifferent' salt, of which neither ion exerts any pronounced physiological action. Sodium chloride will, however, according to its concentration, influence the passage of fluids into or out of the cells. When a red blood-corpuscle, for example, is placed in a hypotonic solution it will swell from entrance of water. If the solution be isotonic, the corpuscle will remain unaltered, as the osmotic pressure inside and outside the membrane will be the same. If the solution be hypertonic, water will pass out of the corpuscle into the surrounding fluid of higher osmotic pressure. Sodium chloride will exert the same effects on other cells, according to its concentration.

If a concentrated (hypertonic) solution be swallowed, it will draw water from the cells of the mucous membrane of the stomach. If the quantity be small, it will be rapidly diluted so that the effect will be transient. If the quantity be considerable, e.g. two drachms, and highly concentrated, this withdrawal of water may so irritate the cells of the mucous membrane as to set up reflex vomiting. Indeed sodium chloride is sometimes so used as a domestic emetic.

If it reaches the intestine in concentrated solution, it will again withdraw water from the mucous

membrane of the gut and so increase the amount of fluid in the intestine. In the case of sodium chloride, however, this effect will only occur in the upper part of the alimentary canal as the salt is rapidly absorbed from the intestine.

The absorbed salt is excreted mainly by the kidneys, and increases the amount of urine. Various explanations have been given of the diuretic effect of salts, and any explanation will depend upon the general theory of kidney secretion. One explanation is that the absorption of salt and water dilutes the blood-colloids and lessens the resistance to filtration through the glomeruli. In whatever way it is brought about, not only such salts as sodium chloride, but other diffusible substances, such as potassium chloride or urea, increase the flow of urine. This effect is more pronounced with 'low threshold' substances. Potassium ions are therefore more diuretic than sodium, and nitrate than chloride. Those salts which are easily absorbed, especially the acetate, citrate, or nitrate of potassium, are sometimes used as **saline diuretics.** *Potassium acetate* is the salt most commonly used, and is given in doses of 15–60 grains, well diluted.

Saline Purgatives.

Ions differ greatly in the readiness with which they are absorbed from the alimentary canal. The chief action of 'diffusible' salts—i.e. salts which are readily absorbed—in medicinal doses is the diuretic action mentioned above. But salts which are 'indiffusible' cannot, when given by mouth, exert this diuretic action, which is dependent upon their being absorbed. If given in sufficient quantity, indiffusible salts act as purgatives. Again, only such salts will be useful for this purpose if their ions have otherwise no pronounced actions which would prevent the salts being

given in considerable amounts. It has been found that of such salts, the kation Mg and the sulphate, phosphate, and tartrate anions are especially indiffusible.

Injected into a ligatured loop of the intestine, water itself or an isotonic solution of sodium chloride is rapidly absorbed, but an isotonic solution of *magnesium sulphate* is not. Magnesium sulphate will not pass easily through the mucous membrane, and water can only be absorbed from the solution to a limited extent, if any, because, as the water is absorbed and the solution therefore becomes more concentrated, greater energy is required to absorb the water against the rising osmotic pressure inside the intestine. The effect of an isotonic solution of magnesium sulphate will therefore be to retard the absorption of water. If the solution is hypotonic, some water will be absorbed from it and thereafter the result will be the same. This is one way in which salts are given as purgatives, i.e. in isotonic or hypotonic solution. The bulk of the intestinal contents is increased and rendered more fluid by the amount of solution given. The increase in the bulk incites reflex peristalsis, and the increased fluidity facilitates the passage of the intestinal contents. A 6 per cent. solution of magnesium sulphate is about isotonic with the body-fluids, and therefore a dose of 6 grammes (90 grains) will retain about 100 c.c. of water in the gut. A dose of 90 grains dissolved in 100 c.c. or more of water is a usual dose for this action of retarding the absorption of water. Purgation usually results in from 1 to 3 hours.

If a hypertonic solution of magnesium sulphate be placed inside a ligatured loop of the intestine, it will draw water from the mucous membrane into the lumen, in addition to preventing absorption of the water in which it is itself dissolved. Larger doses of magnesium sulphate are sometimes given in hyper-

tonic solution with the definite intention of withdrawing water from the body by way of the intestine, or for the secondary effect of diminishing the blood-volume and concentrating the blood.

In the case of magnesium sulphate, both ions are indiffusible, but much the same effects are produced by a soluble salt only one of whose ions is indiffusible, because one ion cannot be absorbed without the other. Thus magnesium chloride and *sodium sulphate*, *sodium phosphates*, and *sodium tartrates* act as purgatives in the same way as magnesium sulphate, and are given in the same doses.

A convenient way of administering these saline purgatives is in the form of an effervescent powder, of which Seidlitz Powder, *Pulvis Sodae Tartaratae Effervescens* (B.P.), *Pulvis Effervescens Compositus* (U.S.P.), may be taken as an example. This powder is dispensed in two packets, one in blue paper containing sodium bicarbonate and sodium potassium tartrate, the other in white paper containing tartaric acid. The first is dissolved in water and the contents of the white packet (previously dissolved by preference) is added to the solution, which is drunk during effervescence. The effervescence is of course provided by the CO_2 liberated from the sodium bicarbonate by the action of tartaric acid. The effervescence not only masks the salt taste to some extent, but is believed to make the powder act more quickly.

When magnesium salts are given by mouth, the systemic actions of magnesium do not come into play, because the small amounts of magnesium that are absorbed are as rapidly excreted. When a magnesium salt is injected subcutaneously or especially intravenously, however, magnesium has a powerful depressing action on the central nervous system. Use has been made of this action, for example, in the case of intra-

spinal injections of magnesium sulphate in the treatment of tetanus.

As has already been mentioned, a red blood-corpuscle will remain unaltered in size if placed in an isotonic solution (e.g. 0·85 per cent.) of sodium chloride, but muscle will soon lose its irritability in such a solution. For maintaining the beat of the heart, as was first shown by Ringer in 1882, a solution requires to contain chlorides of sodium, potassium, and calcium in concentrations similar to those in the blood-plasma. It is now known that such a balanced solution is necessary for the proper functioning of muscle, nerve, and the great majority of tissues. 'Normal saline' solution is therefore only normal as regards its osmotic pressure, and is adequate for purposes where this property alone is of importance; but for the functional activity of the tissues generally, something more than this is necessary, namely a solution of the right osmotic pressure but which contains sodium, potassium, and calcium in correct proportions. Ringer established the composition of such a solution suitable for frog's tissues (i.e. *Ringer's Solution*), and corresponding solutions (e.g. Locke's Solution) have subsequently been determined for mammalian tissues.

Where a large amount of solution has to be injected into a vein, Ringer's solution is preferable to a 'normal saline' solution, as the former is not only correct osmotically but also supplies the plasma with salts in their correct proportions. The necessity for such a fluid arises, for example, after profuse haemorrhage. It was found, however, that Ringer's solution when injected into a vein passes rapidly into the tissues and urine, so that it produces only a transient increase in blood-volume. If, however, to Ringer's solution be added some substance which offers greater resistance to filtration, e.g. 6 per cent. of gum acacia as recom-

mended by Bayliss, the fluid is retained in the vessels for a longer time and also approximates more nearly to the viscosity of the plasma. Such a *gum-saline solution* has therefore been widely used as an intravenous injection in cases of haemorrhage and shock.

III

KATIONS OF THE BLOOD: ACIDS AND ALKALIS

In the previous consideration of the action of water and salts, we have taken account only of osmotic effects, that is, of effects due to the concentration of salts but not due to any specific action; for example, the purgative action of magnesium sulphate is the same in kind as that of sodium potassium tartrate, though it is true that non-absorbability is a more specific property of particular ions. We have now, however, to consider the specific physiological actions of the various kations found in the blood-plasma.

The sodium ion may be regarded as possessing no physiological action.

Potassium

Potassium salts, however, when *injected intravenously* depress the activity of muscular tissues, and in sufficient doses will arrest the heart in diastole. No such results follow the *ingestion* of potassium salts. The amount of potassium in the food of some dietaries may be as much as three ounces, but no depressant effects follow. The reason for this is that potassium salts are so rapidly excreted by the kidneys that the concentration in the blood is not allowed to rise. No depressant effects can therefore be produced by medicinal doses of potassium salts, when given by mouth. For practical purposes of oral administration, so far as the kation of a salt is concerned, a potassium salt will act exactly like a sodium salt except that its diuretic action may be greater.

Calcium

Calcium is normally and constantly present in the blood to the amount of about 10 mg. in 100 c.c. Ringer showed that calcium is necessary for a balanced physiological solution, e.g. for maintaining the beat of the perfused heart. It is now known to be equally necessary for the functional activity of nearly all tissues. A normal diet sufficiently provides for the calcium requirements of the body and for the replacement of the continual loss by excretion through the kidneys and bowel. It is by the selective activity of these organs that the calcium in the blood is kept constant in spite of variations of intake.

No condition is known in which there is any advantage in raising the calcium content of the tissues above the normal. From the limited point of view of therapeutics we may therefore confine our attention to (1) what are the conditions in which the calcium supply to the tissues is defective? and (2) how far can this deficiency be made good by administration of calcium?

In childhood the rapid growth of bones makes unusual demands on calcium, and similarly, during pregnancy, the foetal requirements must be met indirectly through the food of the mother. In those cases it is important that the supply of calcium in the diet, never greatly in excess of the requirements, should be abundant.

Apart from these physiological conditions, there are certain diseases associated with deranged calcium metabolism. In rickets, though the softness of the bones is due mainly to defective calcium deposition, the error does not lie in deficiency of calcium in the food, and consequently the administration of lime salts has, *per se*, little or no beneficial action. In bleeding

diseases, calcium is only of value for increasing the coagulability of the blood in the rare cases where this is associated with low calcium content of the plasma. Tetany is definitely associated with low calcium content of the tissues, and is usually temporarily benefited by injections of lime salts. Calcium salts have an action in diminishing the permeability of animal membranes. In diseases such as urticaria, serum rash, and chilblains, where there is undue permeability of the capillaries, calcium salts are sometimes beneficial.

In such conditions, where the action of calcium after absorption is desired, it is usual to give calcium by hypodermic injection, because lime salts are only slowly absorbed by the mouth. The salt must of course be soluble, and the *lactate*, being less irritant than the *chloride*, is the salt most generally used. It is usually given in doses of 10–20 grains in about two per cent. solution.

Calcium carbonate, an insoluble salt, has long been used in the form of prepared chalk as a remedy for diarrhoea. Especially in acid diarrhoeas in children, it probably acts mainly as an antacid, but it may also diminish the permeability of the mucous membrane of the gut, and thus restrain the excessive passage of fluid into the lumen of the intestine. Chalk (*Creta Praeparata*) is given in doses of 15 grains.

Ammonium

Ammonium is present in the blood only in small amounts and does not possess the physiological importance of sodium, potassium, or calcium. The uncomplicated action of the ammonium ion is naturally displayed most simply by **ammonium chloride**. This neutral salt is freely soluble and, as the ammonium is combined with a strong acid, the salt is

relatively stable and does not smell of ammonia. Given by mouth, ammonium chloride, though it is rapidly absorbed, produces no specific effects of the ammonium ion, because, like potassium chloride, it is so rapidly excreted. If injected intravenously it stimulates the central nervous system, but is not used therapeutically for this. Large doses of ammonium chloride given by mouth cause a reduction of the alkaline reserve of the blood, as it is converted by the liver into urea and hydrochloric acid. It also has a diuretic action.

Ammonium carbonate, in contradistinction to ammonium chloride, is unstable and decomposes rapidly with the liberation of ammonia. Owing to its alkalinity and its liberating NH_3, it is used rather for local actions than for the effect of the ammonium ion after absorption, which can be equally well attained by ammonium chloride.

In the stomach, ammonium carbonate acts as a local antacid and irritates the mucous membrane. It reflexly increases the bronchial secretion like other gastric irritants, and is sometimes used as an expectorant in doses of 5 grains. Larger doses (10–30 gr.) produce emesis. As it is rapidly converted into urea by the liver, ammonium carbonate does not increase the alkalinity of the urine.

The gas NH_3 comes off readily from ammonium carbonate or hydrate. It is an irritant gas, and, when inhaled, irritates the nasal mucous membrane. This irritation produces reflex stimulation of the medullary centres. Ammonium carbonate is thus often used in the form of smelling-salts to stimulate those centres in cases of fainting or collapse.

When a solution of ammonium carbonate is swallowed, similar reflex effects occur from irritation of the mouth and upper part of the alimentary canal. *Spiritus Ammoniae Aromaticus*, which contains am-

monia, ammonium carbonate, and certain volatile oils in alcohol, is a favourite preparation for internal administration. It is given (B.P.) in the usual doses for a compound spirit, i.e. 20–40 minims for repeated, and 60–90 minims for a single administration; U.S.P. 30 minims.

Acids. Acids and Alkalis

Some acids owe their physiological action almost entirely to their acidity, i.e. to the hydrogen ion, and these may be taken together here. In the case of other acids like hydrocyanic acid, the negative ion is so toxic that the part played by acidity is negligible. As the degree of acidity depends upon the amount of dissociation of the acid, the effects to be described will of course vary with the solubility and degree of dissociation. In the case of salicylic acid, which is only slightly soluble and feebly dissociated, the acid action is of relatively little importance.

Strong acids exert a powerful caustic action, due chiefly to their neutralizing alkalis and precipitating some of the proteins. They cause blistering and destruction of the skin, and mucous membranes are even more sensitive to their corrosive action. When swallowed, such acids produce the typical symptoms of corrosive poisoning; pain in the mouth and stomach, vomiting, and collapse.

From the point of view of their medicinal use, the action of dilute acids is of importance especially from the effects they produce on the alimentary canal, blood, and urinary secretion.

Dilute solutions of acids have a characteristic taste, and induce a reflex flow of saliva. Solutions of citric acid or preparations of lemon, which have a pleasant taste and relieve thirst, are used to make a cooling drink in fevers.

The gastric juice is normally acid and contains about 0·2 per cent. of hydrochloric acid. This acid is necessary for activation of pepsin, and the acidity of the contents entering the duodenum also promotes the secretion of the pancreas through the mediation of secretin. No advantage is gained by increasing the gastric acid above the normal, but in diseases where this acid is deficient or absent (e.g. in pernicious anaemia) this defect can to some extent be made good and digestion improved by administration of dilute hydrochloric acid.

Acids are usually absorbed rapidly from the alimentary canal, but do not exist in the blood or tissues as acids, for life is only possible with the reaction of the blood on the alkaline side. The acid is in fact neutralized chiefly by the alkaline bicarbonate of the blood, and the CO_2 evolved stimulates the respiratory centre and is eliminated by the augmented respiration. This diminishes the alkaline reserve of the blood, but this tends to be restored by the excretion of acid salts in the urine. This excretion of acid salts renders the urine more acid.

Acids are not used therapeutically for their action on the blood. The alkaline reserve of the blood can be reduced by administration of ammonium chloride or calcium chloride. The former is changed by the liver into urea and hydrochloric acid: the calcium of calcium chloride is retained or excreted in the intestine as calcium carbonate, and the freed chlorine ions cause an increased acidity, to correct which sodium is excreted as sodium chloride, accompanied by large amounts of water. Both ammonium and calcium chlorides can thus diminish the alkaline reserve of the blood and act as diuretics.

On account of their local and other actions, mineral acids cannot be given in sufficient amounts to produce

any marked or lasting effect on the reaction of the urine. When it is desired to produce such an effect an acid salt, preferably **acid sodium phosphate** (NaH_2PO_4, *Sodii Phosphas Acidus*), which is excreted as such in the urine, can be given in doses of 15–60 grains. As increase of acidity checks the growth of some micro-organisms, acid sodium phosphate may also act as a urinary antiseptic. Any considerable increase in the acidity of the urine cannot, however, be kept up for long, owing to the irritation of the urinary passages which it produces. Acid sodium phosphate is also used to render the urine acid when hexamine (p. 196) is being given, as it is only in an acid medium that hexamine liberates the formaldehyde to which its antiseptic action is due.

For the limited uses of acids themselves, there are official dilute solutions of hydrochloric, sulphuric, nitrohydrochloric, and acetic acids, e.g. *Acidum Hydrochloricum Dilutum*. The usual dose of these dilute acids is about 10–20 minims.

Alkalis.

In the case of the hydrates and carbonates of sodium and potassium, the action of the metal is negligible compared with that of the -OH ion, so that the action of these compounds may be regarded as due entirely to their alkalinity. The hydrates, being more freely dissociated, are more energetic in action than the carbonates or bicarbonates.

Strong alkalis, especially the *hydrates* like caustic potash, are powerful corrosives, chiefly owing to their dissolving proteins and neutralizing acids, and will thus produce destruction and necrosis of tissues with which they come in contact. Solutions of the *carbonates*, while less caustic, can also produce much irritation, especially if they are allowed prolonged action.

Apart from this caustic action, the alkalis, like acids, are of importance chiefly from the effects they produce on the alimentary canal, blood, and urine.

In cases of hyperacidity of the stomach, alkalis, by neutralizing the excess of acid, relieve the pain and eructation. A carbonate is less suitable for this purpose, because the carbonic acid liberated seems to stimulate gastric secretion and therefore to increase the acidity after a temporary diminution. For this purpose, therefore, a carbonate like *sodium bicarbonate*, though widely used as an antacid, is inferior to an oxide like magnesium oxide. Insoluble itself, *magnesium oxide* combines with hydrochloric acid in the stomach to form the soluble magnesium chloride. It therefore not only acts as an antacid but will purge, like magnesium sulphate, if given in sufficient doses. Oxide of magnesium (Magnesii Oxidum) is given in doses of 5 grains frequently repeated, as an antacid, and 20–60 grains as a laxative.

A reduction of the alkaline reserve of the blood (acidosis) occurs in a variety of diseases, including uraemia, diabetes, and shock. In these conditions sodium bicarbonate may produce a temporary improvement. It may be given by mouth (10–30 gr. or more) or intravenously as a 5 per cent. solution.

Alkalis are frequently prescribed in order to lessen the acidity of the urine, especially when this is giving rise to irritation or pain in the urinary passages. For this purpose sodium or potassium bicarbonate can be given (20–30 gr. or more) as they are excreted by the urine as carbonates and so diminish its acidity. They also from their salt action (p. 22) increase the secretion of urine. **Acetates** or **citrates** of sodium or potassium have actions on the blood and urine similar to those of bicarbonates, because the citrates and acetates are oxidized in the tissues to carbonates and

bicarbonates, and are excreted as such. They have the advantage over the carbonates in interfering less with digestion, as they do not so much reduce the acidity of the stomach contents. They are given as alkaline diuretics in doses of 15–60 grains.

IV

DRUGS ACTING ON THE ALIMENTARY CANAL

As drugs are in the majority of cases given by mouth, they naturally have every opportunity of exerting any local action they may have on the mucous membrane of the alimentary canal as they pass through. Also the glands and muscle of the alimentary canal can be influenced in a variety of ways—directly, reflexly, or through their nervous system. Consequently a very large number of drugs have some action on the alimentary canal. Those to be considered here are such as owe their chief medicinal importance to this action. Other drugs, belonging to such different groups as, for example, atropine, pituitary or mercury, have important actions on the alimentary canal, but with these the action on the digestive tube is rather an incident in a wider sphere of action for which they may be more conveniently considered elsewhere.

Drugs acting on the Stomach

Simple Bitters. This group includes a number of drugs which have little in common beyond their bitter taste and absence of physiological action. They are used to improve appetite and to stimulate gastric secretions. This they do reflexly through the sense of taste and most effectively if given shortly before meals. Any substance possessing a bitter taste will do this. Nearly all alkaloids are bitter, but they usually have more important actions. Simple bitters have little action, in medicinal doses, apart from this effect on digestion due to their bitter taste. Those most commonly used are *Calumba* (*Calumbae Radix*), *Quassia*

(*Quassiae Lignum*), and *Gentian* (*Gentianae Radix*). One of the favourite preparations is *Tinctura Gentianae Composita*, which is made from gentian, orange peel, and cardamoms, and has an agreeable aromatic bitter taste. It is given in doses of ½–1 fl. dr.

Pepsin. In the rare cases in which the stomach fails to secrete sufficient pepsin, this ferment may be supplied artificially. In the medicinal form this is obtained from the glandular layer of the pig's stomach and occurs usually in the form of a fine powder which is given in doses of 8 grains.

Acids. Gastric digestion is more often deranged from lack of hydrochloric acid than from lack of pepsin. This occurs, for example, in pernicious anaemia and in carcinoma of the stomach. In these cases dilute hydrochloric acid is given with benefit. It not only supplies the acid necessary for gastric digestion but also provides the acid stimulus for the formation of secretin which stimulates the pancreatic secretions. The official dilute acid, *Acidum Hydrochloricum Dilutum*, contains 10 per cent. of hydrochloric acid and is given in doses of 5–20 minims, well diluted.

Alkalis. In cases where the stomach secretes too much acid (hyperchlorhydria) alkalis can be given to neutralize the excess of acid. For this purpose the bicarbonates of potassium or sodium, or preferably the oxide of magnesium, are most commonly used. They are given in doses of 5–30 grains.

Carminatives. Certain aromatic and volatile substances have been found to aid in the expulsion, by eructation, of gas accumulated in the stomach. This they do apparently by relaxing the cardiac orifice. They thus frequently relieve discomfort due to distension of the stomach. Among the substances used for this action ('carminative' action) may be mentioned volatile oils, e.g. of peppermint, and other

volatile substances such as alcohol, chloroform water, &c. *Wood Charcoal* (*Carbo Ligni*), a fine black tasteless powder, is used for a somewhat similar purpose, but acts in a different manner. It relieves flatulence by its property of absorbing gases. It has no other action and passes through the alimentary canal unabsorbed. It is given in the form of a powder, 15 grains or more, or is sometimes made into lozenges or biscuits.

Drugs acting on the Intestine: Purgatives

Generally speaking, purgatives act either by making the contents of the intestine more fluid or by rendering the movements of the intestine more active, or by a combination of these actions. Such effects can be produced in a variety of ways in accordance with which purgatives can roughly be classified.

The chief normal stimulus to peristaltic activity is the bulk of the intestinal contents, which depends largely upon the amount of unabsorbable material in the food. The latter can be increased artificially by giving with the food some indifferent unabsorbable material. *Agar*, a preparation made from seaweed and consisting largely of unabsorbable gelose, is sometimes given for this purpose. It not only adds to the bulk of the contents of the bowel but also retains water and prevents its absorption. It thus acts as a gentle laxative. It is almost tasteless and is given in doses of about $2\frac{1}{2}$ grains with food or suspended in water.

Liquid Paraffin, *Paraffinum Liquidum* (B.P.), *Petrolatum Liquidum* (U.S.P.), achieves the same purpose in a different way. It is a mixture of liquid hydrocarbons obtained from petroleum and is a tasteless fluid of oily consistency, which is non-irritant and is not absorbed from the intestine. It is given

in doses of 2–4 fl. dr. This adds something to the bulk of the intestinal contents but especially acts as a lubricant. It has been much used in the treatment of chronic constipation.

Sulphur itself has no physiological activity owing to its insolubility in the body-fluids. When taken internally some of it is changed into hydrogen sulphide and other sulphides. These act as mild irritants and increase peristalsis, usually with the passage of a soft formed stool. Milk of sulphur (*Sulphur Praecipitatum*) is thus often used as a mild laxative in doses of 30–60 grains.

[Applied to the skin in ointment, sulphur is partly changed into sulphides, which are destructive to certain animal parasites but have little action on bacteria. In skin diseases due to the former (e.g. Scabies) *Unguentum Sulphuris*, made from sublimed sulphur (*Sulphur Sublimatum*), is often used. In this disease a minute insect burrows into the skin and there deposits its eggs. This causes irritation and itch. The insect can be killed by rubbing sulphur ointment into the skin. This is usually done for 3 or 4 nights and then discontinued, for if applied longer sulphur may cause irritation of the skin.]

Castor oil, *Oleum Ricini*, is a fixed oil obtained from *Ricinus communis*, a plant native to India but cultivated in many parts of the globe. The oil was known to the Egyptians and Greeks, but fell into neglect until Dr. Cavare, a physician of Bath who had practised in the West Indies, recommended it in 1764 as a gentle purgative. Since then it has become widely used as one of the safest and mildest of purgatives.

Castor oil is a pale yellowish transparent viscid liquid, having faint odour and slight but nauseating taste. Like other fixed oils and fats, it is an ester of

a fatty acid—in this case ricinoleic acid—with glycerol. So long as the fatty acid is combined with glycerol the oil is non-irritant, and so can be applied to the skin or even mucous membranes as an emollient. When ingested, it passes unchanged through the stomach, but in the intestine is split up, like other fats, by the fat-splitting ferment of the pancreas (lipase) into its two constituents—glycerol and ricinoleic acid. The freed fatty acid acts as a mild irritant to the gut and so provokes purgation.

It acts in from 2 to 8 hours, and produces soft but not watery motions. It is a very safe purgative and has little tendency to cause griping. Hence it can be used in cases where more violent purgatives are contra-indicated, e.g. in infants, for the aged, and during pregnancy. Its chief drawback is its slight but disagreeable taste and smell. This can be well disguised by giving it with orange juice. The dose is from 2 to 8 fluid drachms for an adult. Half a teaspoonful or more can be given to an infant. Ricin, an albumose which is highly toxic when injected, is present in the castor-oil seeds but not in the oil itself.

Croton oil, *Oleum Crotonis* (B.P.), *Oleum Tiglii* (U.S.P.), is a fixed oil obtained from seeds of Croton Tiglium. This oil contains free fatty acid as well as a highly irritant resin. It is a severe irritant to the skin, and when taken internally produces repeated watery evacuations. It is so irritant that one drop will produce violent purgation. It is now seldom used.

Resinous Purgatives.

Under this heading may be taken a group of purgatives, some of which contain resinous bodies as active principles. In large doses they are liable to produce an inflammatory condition of the mucous membrane of the intestine with colic and repeated watery

purgation. Hence they are sometimes called 'drastic' purgatives, though the intensity of action naturally depends upon dosage. Owing to this irritant action they are not generally suitable for repeated administration, as in chronic constipation. They are quicker in action than the anthracene group, usually producing watery stools in 2–4 hours. Many vegetable substances having this type of action have been used from time to time as purgatives, but on the whole more rarely in recent years. Of those still in occasional use may be mentioned Jalap, Scammony, Podophyllum, Colocynth, Elaterium, and Gamboge, of which Jalap is probably the most important.

Jalapa is the dried tuberous root of certain species of Convolvulaceae which grow in Mexico. The purgative action of Jalap was made known by the early Spanish voyagers. The dose of the powdered root is 5–20 grains, but it is usually given in the form of *Pulvis Jalapae Compositus* (10–60 gr.), which contains also acid potassium tartrate and ginger. This powder, in which the drastic action of undiluted Jalap is somewhat mitigated, is sometimes used as an ordinary brisk purgative. It is also used definitely for its hydragogue action in cases of dropsy, &c. in order to drain off water by the bowel.

A resinous principle, *Jalapae Resina*, extracted from the root, is also used, especially in combination with other purgatives, in doses of 2–5 grains.

Scammoniae Resina (4 gr.) and *Podophylli Resina* ($\frac{1}{4}$ gr.) act very like Jalap resin.

Anthracene Group of Purgatives.

This important group of purgatives, which includes Cascara, Senna, Aloes, and Rhubarb, may be taken together, because each of them owes its action to active principles which are derivatives of Anthracene

($C_{14}H_{10}$). Owing to this similarity in their active principles, they have similar pharmacological properties. They have little action until they reach the large intestine, where they stimulate (probably reflexly) the contractions of the muscle. As they take some time to reach the large intestine, they are slow in action, requiring 8–12 or more hours to produce purgation. As they stimulate the muscular movements, they are liable to cause griping if given alone, but this can usually be prevented by prescribing along with them something which relieves excessive intestinal contractions, e.g. a volatile oil or hyoscyamus. As constipation is frequently due to inertia of the large bowel, these purgatives are frequently used in its treatment, but they should only be used as adjuvants to the more important treatment of constipation, by diet, exercise, and regular habits. Small amounts of the active principles may be absorbed. Chrysophanic acid, one of the anthracene bodies found in rhubarb and senna, may cause a yellowish coloration of the urine, or reddish if it is alkaline.

Cascara Sagrada, the dried bark of *Rhamnus Purshianus*, is one of the mildest of this group, and in the treatment of chronic constipation is frequently given in small repeated doses of the *Liquid Extract* (20–60 min.).

Sennae Folia, the dried leaves of various species of Cassia, shrubs which grow in Africa, India, and elsewhere, have been used for centuries as a purgative. Senna is used in a variety of preparations. *Syrupus Sennae* ($\frac{1}{2}$–2 fl. dr.) is frequently used for children. Compound liquorice powder, *Pulvis Glycyrrhizae Compositus* ($\frac{1}{2}$–2 dr.), owes its purgative action to the Senna and Sulphur contained in it. Liquorice, a sweet substance which gives the powder its name, serves to conceal the disagreeable taste of senna. The powder also

contains fennel, a volatile oil which tends to prevent the griping which senna is liable to produce. This powder is therefore a well-considered combination of ingredients and is an excellent and safe purgative.

Aloe is the dried juice obtained from the fleshy leaves of several species of Aloe, a plant native to Africa but now cultivated in various parts of the world for its medicinal properties. Its purgative action was known to the ancient Greeks, but especially in the nineteenth century it began to be widely used in most European countries. It is even slower in action than the other members of this group, taking usually over 12 hours to induce purgation. It is more liable to produce pelvic congestion than the other anthracene purgatives; it also tends to stimulate the uterus after absorption. It is therefore usually avoided in pregnant women, though the danger of causing abortion is slight with ordinary doses. It is a favourite ingredient of proprietary medicines. It is conveniently prescribed in pill form, e.g. *Pilula Aloes*, 4–8 grains. The dose of aloes itself is 1–5 grains. An active principle, *Aloinum*, given in doses of $\frac{1}{4}$–2 grains, does not seem superior to crude aloes.

Rhubarb, *Rhei Rhizoma*, or *Rheum*, is the dried rhizome of *Rheum officinale*, a plant somewhat resembling garden rhubarb, which grows in China and Tibet. Its medicinal properties were known to the Chinese earlier than 2000 B.C., and it has been imported for centuries into western countries. Unlike the other members of this group, rhubarb contains tannic acid (*v.* p. 45) which has an astringent action. It tends therefore to produce some constipation after purgation and hence is not suitable for repeated administration, e.g. in chronic constipation. It is chiefly used in dyspepsia or diarrhoea due to the presence of undigested material in the alimentary canal, for some cases of

which it has possibly no superior. Of the official preparations, one of the most commonly used is *Pulvis Rhei Compositus*, 10–60 grains. This powder is often called Gregory's Powder from Dr. James Gregory (1753–1821), an Edinburgh physician and a member of a family famous for their intellectual attainments, who first prescribed it. This powder contains, besides rhubarb which acts as a purgative, magnesium oxide which seems to increase the action of rhubarb, and ginger which tends to prevent griping. A drawback to the powder is its disagreeable taste, which it is almost impossible to conceal.

Phenolphthalein (*Phenolphthaleinum*), a synthetic substance which has in recent years been used as a purgative, may be taken with the anthracene group, which it resembles in type of action. It acts chiefly on the large intestine and takes from 6 to 12 hours to act. It is insoluble in water, but is dissolved by bile and alkali in the intestine and produces purgation by mild irritation. Some of it may be absorbed and re-excreted in the intestine, and so its purgative action may last for a few days. It is partly excreted in the urine, to which, if alkaline, it may give a pink colour. In some people phenolphthalein has provoked a peculiar eruption of the skin which may last for months. It is usually given in doses of $2\frac{1}{2}$ grains in powder, pill, or capsule.

In the case of all the purgatives mentioned above, the remedies are given by mouth. Accumulations of faeces in the large intestine can, however, also be got rid of by injections of fluids (*enemata*) into the rectum. An enema of a pint of warm water alone may be used, and acts partly by distending the lower bowel and so provoking peristaltic contraction, and partly by softening the scybala. The action may be increased by adding a slight irritant such as turpentine or soap to

the water. Oil or glycerine may be used for a similar purpose. *Glycerine* acts by withdrawing water from the mucous membrane of the rectum and inducing peristalsis by the resulting irritation. For this purpose it can conveniently be dispensed in the form of a suppository. *Suppositoria Glycerini* are made by incorporating glycerine with gelatine (B.P.) which imparts enough rigidity for insertion but liquefies at the rectal temperature.

Vegetable Astringents: Tannins

Tannins occur in a great variety of plants, ranging from herbs to trees, belonging to different natural orders and found in all parts of the world. Extracts of some of these plants have come to be of great commercial importance from their use in industries, especially of tanning and dyeing. In the process of tanning, the proteins of hides are precipitated by the tannic acid in the plant extract. The tissue (leather) thus becomes hard, dry, and resistant to putrefaction, while retaining much of its flexibility. Some of the plants containing tannic acid have come into medicinal use, and in this case they act also by precipitating proteins. The tannins of different plants resemble one another in chemical constitution and pharmacological action, but, as the slight differences between them influence to some extent their therapeutic uses, it will be convenient first to consider the actions of pure tannic acid.

Tannic Acid, Tannin, *Acidum Tannicum*, is obtained from oak-galls, as a light brownish powder, freely soluble in water, with a characteristic odour, a strongly astringent taste, and an acid reaction. It is a di-gallic acid, gallic acid itself having the formula $C_6H_2(OH)_3COOH$.

Solutions of tannic acid precipitate proteins and

thus, when applied to a mucous membrane or raw surface, coagulate a film on the surface of the cells. This film acts as a protective to an inflamed surface and also lessens the passage of fluids through the superficial membrane. Tannic acid can thus be used for a variety of conditions as an astringent, acting physically in the same way as solutions of metallic salts, e.g. lead acetate (*v.* p. 49). Tannic acid is applied externally in cases of excessive secretion, e.g. weeping ulcers. For such purposes the official *Unguentum Gallae* (B.P.) or *Unguentum Acidi Tannici* (U.S.P.) is convenient.

In the mouth tannic acid produces, in addition to a harsh bitter taste, a feeling of dryness and roughness due to coagulation of the superficial layers of protein. It is used for tonsillitis and relaxed sore throat. It also checks bleeding from the gums. This it does by coagulating the blood-proteins and so favouring the formation of normal clotting. For exerting its action on the mouth and throat the official *Trochiscus* may be used, or the *Glycerinum* may be employed as a paint or diluted as a gargle.

When swallowed, tannic acid exerts an astringent action on the stomach and intestine and tends to produce constipation. The coagulation of the proteins of the epithelium lessens the secretions of mucus and also, by protecting the surface, diminishes the effect of the gut-contents in starting the peristaltic reflex. Owing to this delay in the passage of the contents, longer time is given for reabsorption of water. Tannic acid also combines with the proteins of the food, but is liberated again in the process of their digestion.

Most of the tannic acid is decomposed in the gut into gallic acid, which is devoid of astringent properties. In the blood it exists as alkaline gallates and tannates, which also have no astringent action. Tannic acid has

therefore no astringent effect on distal bleeding, e.g. from the lung or kidney.

Many other tannin-containing plants, e.g. *Hamamelis* (Witch Hazel), *Krameria* (Rhatany Root), are used to furnish preparations which are used for much the same purpose as tannic acid itself. Two plant-extracts, *Kino* and *Catechu*, are superior to pure tannic acid in the treatment of diarrhoea, because the variety of tannic acid which they contain is less rapidly destroyed in the intestine and therefore exerts an astringent action farther down the gut. These may be used in the form of *Tinctura Kino* or *Tinctura Catechu* (each $\frac{1}{2}$–1 fl. dr.). The B.P. preparation *Pulvis Kino Compositus* (5–20 gr.), containing kino which acts as an astringent, and opium and cinnamon which relieve colic, is specially designed for the treatment of diarrhoeas.

V

HEAVY METALS

Just as the heavy metals have certain chemical resemblances whereby they form a group, so one might anticipate that they would have some common pharmacological properties. It is only, however, in their local actions that they show close pharmacological similarities. Moreover, some metals are, under ordinary conditions of medicinal use, not absorbed at all or at least not to a degree sufficient to produce recognizable physiological actions, and therefore only their local actions need be considered. When the heavy metals are considered as a group, the division of their actions into local and general is therefore unusually helpful, in the first place because local actions are the only effects that some of them ordinarily produce, and in the second place because it is in these local actions that different metals resemble one another. It is convenient in the first place to consider these local actions so far as they are common to metallic salts, and thereafter to take up the metals individually.

Local Actions of Salts of Heavy Metals

When a soluble salt of heavy metal is added to a solution of albumen, a precipitate is formed which is the albuminate of the metal. Protein, which is amphoteric, acts in this reaction as an acid, forming an insoluble salt of the metal. There are three pharmacological actions obtainable from such metallic salts which depend upon this interaction with proteins, viz. astringent, caustic, and antiseptic actions. Of these, the astringent action depends solely upon the actual physical coagulation of the proteins, whereas the

caustic and antiseptic actions are due at least as much to the toxic action of the metals on the cells, independent of whether the protein is coagulated or not.

When a solution of heavy metal is applied to a mucous membrane, a film of the surface is coagulated. If the solution be strong, this may lead to an opacity of the surface which may be obvious on inspection.

When a stick of solid silver nitrate is drawn across the red granulating surface of a wound, it leaves a white wake of coagulation, giving the appearance as if one had drawn a white chalk over a red surface. When a dilute solution of silver nitrate is applied to a mucous membrane, the coagulation of proteins will not be so intense and no change in the surface may be apparent to naked-eye observation. At least two effects may result from this coagulation of the surface film of the cells. In the first place the surface may be drawn together, puckered in fact, and this was the original meaning of the word astringent. In the second place the permeability of the cell surface will be altered. If a solution of lead acetate or of tannic acid, either of which coagulate proteins, be applied to a mucus-secreting surface like the mucous membrane of the trachea, the cells become more opaque and the secretion of the mucus diminishes. One of the chief uses of astringents is to produce this effect of diminishing exudation or secretion from mucous membranes or raw surfaces.

So long as this coagulation of the surface film of the cells is not too intense, it can be imagined that the effects will be confined to those changes in permeability already described. The interchange of substances necessary for the life of the cell can still take place through the unaltered deep surfaces of the cells. If however the coagulation is too intense, or if the metal penetrates to the cell nucleus, the cell may die.

In this case the metallic salt exerts a 'caustic' action, that is to say there is an actual destruction of cells, and the dead cells are shed off. The difference between astringent and caustic action may be therefore one only of degree.

So far, the results of the application of a metallic salt have been considered only from the point of view of the tissue-cells. If, however, there be a bacterial infection of the surface, the proteins of the bacterial cell will be subject to the same changes as the proteins of the tissue-cells; and as the entire surface of a bacterium may be exposed to the metallic solution, it may presumably be more seriously endangered than the tissue-cells which are exposed on one side only.

Actually, however, even in superficial bacterial infections, the micro-organisms are more or less embedded in the tissues, so that bacteria and tissue-cells are almost equally exposed to the antiseptic solution. It is therefore difficult, with metallic solutions and indeed with most antiseptics, to find a concentration that will inhibit bacterial growth without doing some damage to the tissue-cells.

As these local actions depend upon interaction between metallic ion and protein, the intensity of this action will vary with the degree of ionization and the solubility of the salt employed. Insoluble metallic compounds may also combine with proteins, but more slowly and less completely. Such insoluble compounds therefore exert much feebler, but sometimes more prolonged, local actions.

Copper

Cupri Sulphas is the only official salt of copper. It is freely soluble in water and the solution is acid. It has the local actions already described as characteristic of soluble salts of heavy metals. It is caustic in

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solid form, or in very concentrated solution. Weaker solutions are astringent and antiseptic. It is used chiefly as an antiseptic and astringent for mucous membranes, such as the conjunctiva or urethra.

Internally it is used chiefly as an emetic. It irritates the stomach by combining with the proteins of the mucous membrane. If sufficient copper sulphate be given to produce the requisite amount of irritation (5 to 10 gr., i.e. the emetic dose of it) then reflex vomiting will be set up. It is important to remember that this is not merely a reflex through Auerbach's plexus, but through the vomiting centre. The efferent impulses from this centre start the whole complicated machinery of vomiting, not only the opening of the cardiac orifice of the stomach and the reversal of gastric peristalsis, but also the contraction of the diaphragm and of the muscles of the anterior abdominal wall, whereby the stomach is emptied by pressure from without. Copper sulphate is a relatively speedy emetic, generally producing vomiting in 10 to 20 minutes.

In prescribing it as an emetic, it will be fairly obvious that certain conditions will have to be complied with, and these conditions have to be observed in the case of any emetic which acts by irritation. One would not, for example, prescribe it as crystals or even as powder, for it would thus exert a caustic action on the oesophagus and stomach; one would prescribe it in solution. The actual strength of solution will be of importance; it must not be too strong, otherwise it will cause an undue amount of irritation; it must not be too weak, otherwise it will not cause sufficient irritation to cause vomiting. A suitable strength of solution to cause vomiting is about one per cent.

Copper sulphate has a special use in phosphorus poisoning. It forms an insoluble and almost inert

phosphide of copper, and so diminishes the toxicity and delays the absorption of phosphorus.

Zinc

The actions of soluble salts of zinc are almost identical with those of copper sulphate. The chloride, sulphate, and acetate are all official and all soluble. The chloride is used almost only as a caustic, the sulphate and acetate as astringents and antiseptics. The latter are less irritant than copper sulphate and are therefore more widely used as applications, in solution, to the eye, ear, and urethra. For the eye zinc sulphate may be used in a strength of 0·1 to 1·0 per cent., and for the urethra about four times as strong.

Zinc sulphate is also used as a reflex emetic, and, as it is less irritant than copper sulphate, the dose required to produce emesis is larger, viz. 10–30 grains.

In addition to these soluble salts, the insoluble oxide (*Zinci Oxidum*) and carbonate (*Zinci Carbonas*) are also used. Being insoluble, they combine only slowly with proteins, and consequently exert a less energetic but more prolonged local action than the soluble salts. They are chiefly used as astringents and antiseptics, in lotions and ointments, for skin diseases. *Unguentum Zinci*, an ointment made from zinc oxide, is a widely used official preparation.

Aluminium

The salts of aluminium have actions similar to those of copper and zinc. *Alum* (*alumen*) is a double sulphate of aluminium with either potassium or ammonium. It is used locally as an astringent-antiseptic, and internally as an emetic in doses of 10–30 grains in solution. *Aluminium acetate* (N.O.) is frequently used in solution as an astringent antiseptic, e.g. for burns.

Silver

Argenti Nitras is the only official soluble salt of silver. It forms a dense coagulum with proteins and is also precipitated by the chlorides in the tissues. Its astringent action is therefore powerful but superficial. Concentrated solutions are caustic, but, for the same reasons, not penetrating. Silver nitrate is also a powerful antiseptic.

Externally it is used in dilute solution as an astringent-antiseptic. It is of especial value as an application to mucous membranes, such as the conjunctiva and urethra. The strength of solution used varies with the sensitiveness of the surface to which it is applied, and ranges from 0·02 to 2·0 per cent. It is used commonly in the form of a solid stick (*Argenti Nitras Induratus*, B.P.; *A. N. Fusus*, U.S.P.) as a caustic, possessing the advantage that its extent of action can be limited.

Given by mouth it has been used as an astringent in gastric ulcer. It has no astringent action on the intestine, as it is precipitated in the stomach as silver chloride and reduced to metallic silver in the intestine. Dilute solutions have been used successfully as enemata in some forms of chronic dysentery.

When small quantities of silver are continuously administered (as was formerly done in the treatment of chronic nervous diseases), the metal may be absorbed in sufficient quantity to give rise to definite symptoms, '*Argyria*'. It is stored up as an organic compound chiefly in the connective tissues. This compound has a dark colour, and the tissues in which it is stored become pigmented. This pigmentation may occur in any organ, but for practical purposes the most important seat of deposit is the skin, which displays a greyish or slate colour. This colour, once produced, cannot be removed. Local pigmentation has

occurred from the continuous application of silver nitrate to mucous membranes.

Colloidal Compounds of Silver.

One disadvantage attending the use of silver nitrate as an astringent or antiseptic is the amount of irritation it produces, due to its combining with the proteins of the tissues. To obviate this, compounds have been introduced in which the silver is already united with protein, so that little or no silver is in an ionizable form to unite with the tissue protein. Such compounds are much less irritating than silver nitrate, but, as the antiseptic action is also dependent upon ionizable silver, they are also less antiseptic. For some purposes, e.g. for gonococcal infection of the urethra, they are preferable to silver nitrate itself.

The British Pharmacopoeia does not yet recognize these protein compounds of silver, but the U.S. Pharmacopoeia contains two preparations. *Argento-Proteinum Forte* contains about 8 per cent. of silver, partly in an ionizable form, and is used in a strength of 0·25 to 1·0 per cent. 'Protargol' is one form of this strong silver-protein. *Argento-Proteinum Mite* contains about 20 per cent. of silver, but this is almost entirely in a non-ionizable form, so that stronger solutions, e.g. 10–25 per cent., can be used. 'Argyrol' is one form of this weak silver-protein.

Lead

Plumbi Acetas is the most important soluble salt of lead. It differs from the soluble salts of the metals previously considered chiefly in being less irritant and having less antiseptic power. It is however an active astringent, producing a dense precipitation of proteins. As it is also precipitated by chlorides in the tissues, its action is superficial, which is usually desirable in an astringent.

Solutions of acetate of lead are applied for their astringent and sedative action to the skin and mucous membranes. Of the heavy metals, it is the most efficacious as an intestinal astringent, and is occasionally used to control diarrhoea, dose 1–5 grains. For this it is usually given in pill form combined with opium, as the official *Pilula Plumbi cum Opio* (2–4 gr.). In this combination, lead acetate diminishes the intestinal secretion, while the opium slows the movements of the alimentary canal and relieves colic if present.

Preparations containing lead in the form of subacetate (*Plumbi Subacetas*), which is even more astringent than the acetate, are also used for their local astringent action, but only externally.

Chronic lead poisoning. Lead, like silver, can, if it gains entrance into the body in small amounts over long periods, produce chronic poisoning. Owing to its frequency and the variety of symptoms to which it may give rise, chronic lead poisoning is of great importance and may be induced in many ways. Of the commoner causes may be mentioned the drinking of water, beer, or cider contaminated with lead, or the swallowing or inhalation of lead in some form by lead workers, plumbers, compositors, or painters. The condition may, however, arise in a great variety of ways, some not readily detected. In nearly all cases small quantities of lead compounds have been ingested or inhaled (as powder) for a considerable time, and, though absorption is slow and incomplete, excretion is even less rapid, and the metal accumulates in the tissues, giving rise to toxic effects.

The symptoms are so numerous that it is possible here to enumerate only the most important. Among the early and fairly constant symptoms are loss of appetite, constipation, and the appearance of a blue line at the margin of the gums due to the formation

there of sulphide of lead. The 'blue line' may be present without any other symptom of lead poisoning and, as it always disappears slowly, is of considerable diagnostic value. A peculiar basophilic change in the red blood-corpuscles often occurs early, and is very significant of lead poisoning.

The nervous system, both central and peripheral, is especially prone to be attacked by lead. The most common result of this is peripheral neuritis, which usually first affects the nerves supplying the extensors of the wrists and fingers but spares the brachio-radialis. Sometimes the muscles of the foot and other muscles are affected. The sensory nerves may be also affected, giving rise to areas of hyperaesthesia or anaesthesia.

Lead has also a stimulant action on smooth muscle, giving rise to three effects of importance. Intestinal colic, characterized by the onset of severe, often sudden, pain, commonly referred to the umbilicus and usually relieved by pressure, is a common symptom. It is believed to be due, in part at least, to a direct irritant action of lead on smooth muscle. In women suffering from lead poisoning, abortion is frequent, and lead (often in the form of lead plaster taken by mouth) is sometimes used as a criminal abortifacient. It is never used medicinally for this effect on the uterus, which is ascribed to the stimulant action on the uterine muscle. The occurrence of arteriosclerosis and high blood-pressure in chronic lead poisoning may be due to a similar action on the arterial muscle.

Mercury

Mercury is used medicinally in the form not only of mercuric and mercurous compounds but also of preparations of metallic mercury itself. However combined, mercury always exerts qualitatively the same

action, but the intensity and rapidity of action are modified by the degree of solubility and dissociation of the particular compound used. Thus the actions of mercury are much more rapidly and energetically displayed by the perchloride, which is soluble, than by the subchloride, which is insoluble.

Local Actions. It is convenient first to consider the action of a soluble mercuric salt like the perchloride. Perchloride of mercury or corrosive sublimate ($HgCl_2$) is soluble 1 in 16 in water. It precipitates proteins, but this precipitate is more readily soluble in excess of protein than are the albuminates of most heavy metals. Hence solutions of corrosive sublimate are almost non-astringent, because, compared with the amount of mercury used, an excess of protein is likely to be present, so that no permanent coagulum is formed to produce an astringent action. Moreover, whereas depth of local action of soluble silver and lead salts is prevented by their precipitation as chlorides, this does not happen with corrosive sublimate, which is itself a soluble chloride. The latter is therefore a much more penetrating caustic, so that the depth of action is difficult to control. Hence mercury is rarely used medicinally as an astringent or caustic. On the other hand, in antiseptic action mercury excels the other heavy metals, this superiority being due partly to its more ready penetration into cells. Mercuric chloride is an important antiseptic. As is true of all antiseptics, some bacteria are more resistant to it than others so that higher concentrations are required to kill these, but corrosive sublimate is generally used in the concentrations of 1 in 20,000 to 1 in 2,000 as an antiseptic.

Other soluble salts of mercury act similarly, their activity depending greatly upon the degree of ionization, mercuric cyanide, which dissociates slightly, being a feebler antiseptic than mercuric chloride, which

dissociates readily. Insoluble salts of mercury, e.g. calomel, and oxides of mercury, combine much more slowly with proteins and exercise a weaker but more prolonged antiseptic action.

These compounds show corresponding differences in the intensity of their local actions on the alimentary canal. Thus the soluble perchloride is a severe irritant, producing diarrhoea in small doses, whereas much larger doses of calomel are required to produce this effect. The dose of corrosive sublimate (*Hydrargyri Perchloridum*) is $\frac{1}{64}-\frac{1}{16}$ grain, whereas that of calomel (*Hydrargyri Subchloridum*) is 1–5 grains. That eighty times as much of the latter can be given as of the former is due to its insolubility, and is in spite of the fact that it contains, weight for weight, more mercury than the perchloride.

Mercury is, compared with the metals previously considered, readily absorbed. It tends to be stored in the body, especially in the kidneys and liver, and part of the absorbed mercury is excreted very slowly. It is eliminated by nearly all excreting glands, especially by the kidneys and by the gut, but also in the saliva, milk, &c. Owing to the slowness of its excretion it is liable to accumulate in the body and to produce toxic effects if given continuously. Usually, in small doses, it excites to greater activity the glands by which it is excreted. Single medicinal doses usually produce no marked effects, except possibly diarrhoea and increased diuresis. Beyond these effects it is chiefly the toxicology of mercury that is important, namely the toxic effects produced by a single large dose or by long continued small doses.

In *acute poisoning* by ingestion of a soluble salt like the perchloride, the symptoms come on within a few minutes—pain in the throat, gullet, and abdomen with frequent vomiting and purging, the evacua-

tions being usually streaked with blood. Symptoms of collapse follow of the usual type consequent upon corrosive irritation of the alimentary canal. Death may occur in a few hours, but usually in from one to five days, and occasionally even later. When death is delayed the symptoms merge into those of chronic poisoning due to absorption of mercury, suppression of urine due to nephritis being the main cause of a fatal issue.

Chronic poisoning from continued absorption of small quantities is of greater importance, because it may arise during medicinal administration. During the treatment of syphilis with mercury, watch must be kept for the appearance of any symptoms of overdosage. An early symptom is increased salivation, probably due to irritation of the salivary glands by the mercury which they excrete. The amount of saliva secreted may be enormous. Soreness of the gums, loosening of the teeth, and even gangrene of the cheek may also occur. Formerly a mild degree of these symptoms, such as slight salivation and tenderness of the gums, was anticipated in the routine treatment of syphilis by mercury; now they are as far as possible avoided. There are often present also symptoms of irritation of the stomach and intestine, loss of appetite, nausea, and diarrhoea.

The urine may be at first increased, but later nephritis is often set up with albuminuria. Especially in the late stages of acute poisoning there may be marked diminution, or even complete suppression, of the urine. Actual necrosis of the kidney epithelium may be induced, with deposit of calcium phosphate and carbonate in the necrosed cells.

Skin rashes not uncommonly occur with mercury, most frequently when it is applied externally but also from any other method of administration. Rarely by

long-continued medicinal administration, but more often in workers with mercury, a kind of chronic poisoning may arise which is usually ushered in by symptoms of subacute poisoning, but which eventually affects chiefly the central nervous system. The chief symptoms are tremor of certain muscles, usually affecting the muscles of the face and hands first, and consisting of fine movements aggravated by voluntary effort. Later the movements may become continuous and epileptiform in nature. Various sensory disturbances have also been described, as well as a peculiar type of nervous irritability (erythysmus mercurialis). Nervous symptoms are most liable to occur when mercury is inhaled in toxic quantities.

Therapeutic uses of Mercury. Compounds of mercury have a wide use as *antiseptics.* Soluble salts, like perchloride, are used to disinfect the hands, &c., but they are irritant to delicate tissues, such as serous membranes, and they corrode steel instruments. Insoluble preparations are used in the form of lotions and ointments as antiseptics for syphilitic lesions, skin diseases, &c. Black and yellow wash (*Lotio Nigra* and *Lotio Flava*), which contain a suspension of mercurous and mercuric oxides respectively, are used as local applications in syphilitic lesions. Ointments of *Ammoniated Mercury* (*Unguentum Hydrargyri Ammoniati*) or of *Mercuric Oxide* (*Unguentum Hydrargyri Oxidi Flavi*) are used in skin infections. There are many other official preparations of mercury for external use as antiseptics.

Internally mercury in the form of calomel, *Hydrargyri Subchloridum,* is used as a *purgative* and intestinal antiseptic. Being insoluble, its action on the intestine is milder than that of the perchloride. Grey powder, *Hydrargyrum cum Creta,* a mixture of metallic mercury and chalk, which is even milder in action than calomel,

is used for the same purpose especially in children. Both calomel and grey powder are given in doses of 1–5 grains.

Calomel is also used as a *diuretic*, especially in cases of dropsy due to heart disease. More recently a compound of mercury with barbital, called 'novasurol', has been used by intravenous injection as a diuretic. It is a more powerful diuretic than calomel.

The chief purpose for which mercury is given with a view to its action after absorption is, however, in the treatment of *syphilis*. It has been used in the treatment of syphilis for over four centuries, and acts by destroying the causal organism of the disease. Mercury can be administered for this purpose in a variety of ways, of which the following are the most important. (1) *By ingestion.* This is the most convenient method, but is apt to produce alimentary disturbances. Calomel and grey powder are convenient preparations. (2) *By inunction.* If an ointment of mercury is rubbed into the skin, the metal is absorbed by the sebaceous glands. This absorption is more rapid if the ointment basis be an animal fat as in blue ointment, *Unguentum Hydrargyri*, which is often used for this purpose. This method minimizes the digestive disturbances that mercury is apt to set up but is rather disagreeable, and the amount of absorption by the skin is uncertain. (3) *By injection.* Subcutaneous injection is painful, and liable to produce abcess; intravenous injection is more dangerous and liable to induce nephritis; so that mercury is usually injected intramuscularly. Various preparations are so used, a suspension of mercury in a mixture of lanoline and oil being a favourite preparation. Injections are given, usually into the gluteal muscles, weekly for several weeks.

The syphilitic infection is subdued but usually not entirely eradicated by mercury. Arsenic, in the form

of arsenobenzol, acts more rapidly, and generally both methods of treatment are combined.

Iron

Iron differs from the other heavy metals in being an important normal constituent of the body. In mammals most of the iron is contained in the haemoglobin of the blood and is essential for its formation, but traces of iron are found in all tissues and are probably necessary for the life of all cells.

Local Actions of Iron Salts. As antiseptics, compounds of iron are inferior to those of other heavy metals and are therefore rarely used for this purpose. *Ferric chloride* precipitates proteins, but solutions of it are too acid and irritating for general use as astringents. They are occasionally used for the local arrest of haemorrhage, which they tend to bring about by coagulating the proteins of the blood and thus favouring the development of normal clotting. Ferric chloride does not constrict the blood-vessels and is generally inferior to adrenaline as a styptic. When given by mouth it has of course no effect on distal bleeding, e.g. from the lung or kidney. Ferrous salts are less astringent than ferric. The local actions of iron salts are therefore, from the therapeutic point of view, unimportant.

General Actions of Iron. When iron salts are given by mouth, most of the iron passes unabsorbed through the alimentary canal; and the small amounts that are absorbed are insufficient to produce any immediate effect or indeed any measurable effect unless in cases of iron deficiency. For practical purposes, therefore, the pharmacology of iron resolves itself into the action of iron in abnormal conditions of iron metabolism, especially in deficiency of haemoglobin.

The total amount of iron in the body of an adult

man is about three grammes, most of it being in haemoglobin. There is a continual and inevitable, though small, daily excretion of iron, resulting indirectly, for example, from the continual destruction of red blood-corpuscles. This amount is about 5 milligrammes, most of which is excreted by the large intestine (through the mucous membrane), but traces are found also in the urine. Though this daily loss of iron is small, it must be remembered that it is considerable in proportion to the total iron of the body. For example, it would be equivalent to the excretion of all the iron of the body in about two years. This daily loss is, however, compensated by the absorption of iron from the food. As iron is a necessary constituent of most vegetable and animal tissues, it follows that nearly all foods contain it in small quantities. As iron is essential for the life of mammals, it goes without saying that the amount of iron in the food is normally adequate, otherwise the animals could not have survived in this dependence. The amount in the daily diet will obviously depend upon the amount and nature of the food, but the interesting point is that a normal well-regulated diet does not contain any enormous excess of iron. It has been estimated at about 10 milligrammes per day, i.e. about twice the inevitable daily loss.

An ill-balanced diet, especially if deficient in meat or vegetables, may easily contain too little iron, and in such cases it is important to make good this deficiency by administering iron salts.

Iron is absorbed by the small intestine and is then stored in the spleen and liver. In the latter it is built up into compounds which are probably precursors of haemoglobin. These compounds, liberated into the blood, are taken up by the bone marrow where the final synthesis of haemoglobin takes place. Iron

which is absorbed in excess of the body requirements is excreted by the mucous membrane of the large intestine. Only a small proportion of the iron ingested is absorbed.

Therapeutic uses of Iron Salts. Chlorosis, a form of anaemia in young women, is characterized by a reduction in the total number of red cells with a disproportionate reduction in the percentage of haemoglobin. That is to say that each red cell contains less than the normal proportion of haemoglobin. Iron produces a conspicuous improvement or cure of this disease. Chlorosis has, however, in recent years become an increasingly rare disease, and the therapeutic importance of iron, which was used mainly in this disease, has correspondingly diminished. Iron is, however, still valuable when there are unusual demands upon it, e.g. in pregnancy, after haemorrhage, in rapidly growing children, or in convalescence from various diseases.

In all these conditions it must be remembered that the improvement in the blood occurs slowly. The human red corpuscle, which has lost its nucleus, cannot synthesize haemoglobin. Consequently the rise in percentage of haemoglobin can occur only from the formation by the bone marrow of new red cells, containing an increased amount of haemoglobin, gradually replacing the red cells which are normally and regularly being destroyed. This replacement process takes time, usually some weeks.

Of the large number of official preparations of iron, many are superfluous. For internal use reduced iron, *Ferrum Redactum* (1–5 gr.), or *Pilula Ferri*, Blaud's Pill (5 gr.), or a 'scale' preparation such as *Ferri et Potassii Citras* (3–10 gr.) is most commonly used. Ferric preparations, e.g. *Tinctura Ferri Perchloridi* (5–10 min.), are more astringent and more liable to produce constipation.

VI

METALLOIDS

It is convenient to take together a group which consists of bismuth, antimony, arsenic, and phosphorus. They form a series in which the resemblances to the heavy metals diminish as we proceed from bismuth to phosphorus. Indeed, bismuth and antimony are often included among the heavy metals proper.

Bismuth

All the official salts of bismuth are insoluble in water, and they do not therefore have the immediate precipitant action on proteins and the resulting local actions which are characteristic of the soluble salts of the heavy metals. The local actions of the bismuth salts are indeed largely dependent on the fact that the bismuth salts occur in the form of very fine insoluble powders. These are used externally as dusting powders and internally as sedatives in dyspepsias and diarrhoeas. They act mechanically by coating over the surfaces and possibly also by adsorbing toxins. When given by mouth, only traces of bismuth are absorbed—not enough to produce general effects.

Bismuth compounds are also used as applications to wounds and ulcers. From these bismuth may be absorbed and produce poisonous effects.

More recently bismuth compounds have been injected intramuscularly in the treatment of syphilis and other protozoal diseases. They have a more rapid curative action than mercury, but less rapid than that of organic preparations of arsenic.

The chief symptoms of chronic poisoning (caused e.g. by slow absorption from a wound) are nausea, albuminuria, ulceration of the gums, and a dark patchy discoloration of the mouth and throat.

For internal use, *Bismuthi Subnitras* or *Bismuthi Carbonas* (both 5–20 gr.) are chiefly used. Suspensions of the oxide or of the metal itself are among the most favoured preparations for intramuscular injection.

Antimony

Antimony, in the form of tartar emetic, has had a chequered career as a therapeutic agent. From the early part of the seventeenth century onwards it was used for a great variety of diseases, in many of which its value was hotly disputed. During the nineteenth century its reputation waned, but in this century new and established therapeutic uses for it have been discovered, which have brought it back again to a pride of place among remedial agents.

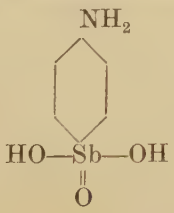
Tartar Emetic (*Antimonium Tartaratum*, B.P.; *Antimonii et Potassii Tartras*, U.S.P.) forms colourless crystals or a white powder with a disagreeable metallic taste, soluble 1 in 17 of cold water.

Tartar emetic is an irritant even to the skin, but more so to mucous membranes. Taken internally in doses of $\frac{1}{2}$–1 grain, it produces reflex emesis, from irritation of the gastric mucous membrane. Vomiting does not usually occur before 20–30 minutes, and is apt to be repeated. The usual concomitants of nausea, especially increased bronchial and sweat secretion, are conspicuously exhibited. These secondary effects of gastric irritation can be produced by doses too small to produce actual vomiting, and in such doses, e.g. about $\frac{1}{12}$ grain, tartar emetic is used as an expectorant and diaphoretic. It was formerly widely used as a diaphoretic in fevers, but has been largely supplanted by newer artificial antipyretics. As an expectorant it has given place to ipecacuanha, which has a similar but milder action.

So far as these actions are concerned it might therefore have become by now a superfluous remedy, had it

not in recent years been discovered to possess a singular and specific remedial effect in certain infections. The beginning of this new phase in its history was the discovery, about twenty years ago, that antimony has a powerful trypanocidal action. Owing to its local irritant action, tartar emetic cannot be given by mouth or subcutaneously in sufficient quantity to be effective. It was soon found, however, that it can be given successfully by intravenous injection. So given, it has a much wider range of parasiticidal activity than arsenic. It is of some value in the treatment of trypanosomiasis, but has been found even more useful in leishmaniasis and schistosomiasis. In the former, e.g. Kala-Azar, it has changed a 90 per cent. mortality into a 90 per cent. recovery; and in the latter, e.g. Bilharzia infection, it has also proved a specific cure. A disease due to yet another type of infection, Granuloma inguinale, also yields to antimony therapy.

These diseases usually require repeated intravenous injections. Such a course may begin with a dose of $\frac{1}{2}$ grain, increasing to 2 grains, and given thrice a week. Sodium antimonyl tartrate, which is less toxic, more soluble, and cheaper than tartar emetic, has now largely replaced the latter for intravenous injections. It is still the favourite antimony compound for the treatment of bilharziasis. In the last five years or so, some *pentavalent compounds of antimony*, derivatives of para-amino-phenyl stibonic acid



have been used. This substance is the antimony equivalent of atoxyl (p. 71). These compounds have proved especially useful in the treatment of Kala-Azar. They are given intravenously.

Arsenic

The modern use of arsenic as a therapeutic agent began substantially with the publication in 1786 by Thomas Fowler (1736–1801), a physician of Stafford, of *Medical Reports on the Effects of Arsenic in the Cure of Agues*, &c., and with the aid of an apothecary, Hughes, he compounded a substitute, *Liquor Arsenicalis* (still called Fowler's Solution), for the quack remedy then known as 'Tasteless Ague or Fever Drops'. Nearly a century and a half has elapsed since Fowler's work was published, and in that time preparations of arsenic have been tried in a great variety of diseases. Especially within the last twenty years, organic compounds of arsenic have acquired a great importance in the treatment of syphilis and trypanosomiasis.

Arsenious Acid, As_2O_3 (*Acidum Arseniosum*, B.P., *Arseni Trioxidum*, U.S.P.), occurs usually in the form of a white powder or porcelain-like masses. It dissolves slowly in rather less than 100 parts of cold water. It is almost tasteless and odourless.

Arsenious acid is a caustic. It does not combine with proteins like the heavy metals, and its caustic action is slower than that of corrosive sublimate, for example.

When taken internally it does not produce any obvious effects in single medicinal doses. From the pharmacological point of view it is convenient, therefore, to consider first the action of single toxic doses and secondly the action of continued smaller doses.

Acute poisoning. As one would expect of a caustic substance, arsenious acid causes severe irritation of the stomach and intestine, with vomiting and profuse

and repeated watery diarrhoea. Secondary symptoms supervene, resulting from the rapid loss of fluid and the dilatation of the abdominal vessels, e.g. thirst, diminution or suppression of urine, low blood-pressure, and collapse, with coldness and pallor of the skin and rapid feeble pulse. In acute fatal poisoning, death may occur within twenty-four hours, but is usually postponed for two or three days, when the patient dies of exhaustion. If the dose is smaller than the lethal dose, recovery may occur without symptoms other than those described, but more or less marked symptoms due to absorbed arsenic are also apt to occur. If the quantity absorbed be large, fatty degeneration of the liver and other organs is a usual result.

When smaller quantities are ingested over long periods, *chronic poisoning* due to absorbed arsenic may ensue. This may happen from prolonged medicinal dosage, from accidental contamination of wines, beers, sweets, &c., with arsenic, or in a variety of other ways. The following are among the common effects of chronic poisoning. There may be dyspepsia, nausea, or diarrhoea. An important early diagnostic symptom is redness and itching of the conjunctiva, and a catarrhal condition of the upper air-passages, with sneezing or coughing. A variety of skin eruptions may occur, and the epidermis may be shed off in fine brownish scales or flakes. A leaden-coloured pigmentation of the skin is not uncommon. Usually at a later period, symptoms may appear from peripheral neuritis. This may affect sensory nerves, causing various disturbances of sensation, and also motor nerves, producing paralysis of voluntary muscles, the first sign of which is usually disappearance of the ankle-jerk. If the ingestion of arsenic is stopped, recovery may be complete, but not of course if the muscles have degenerated.

Arsenic is excreted slowly, some of it within a day

or two in the faeces, but much of it is stored for an indefinite time in the tissues, and eliminated in the hair, epidermis, &c.

Therapeutic Uses of Arsenic. Arsenic has been used in the treatment of many, generally chronic, diseases. The aetiology of some of these diseases is still unknown, so that in them it is not yet possible to give an explanation of the remedial action of arsenic. It is of value in some chronic superficial skin diseases, e.g. psoriasis and chronic eczema. Here it may act by improving the condition of the skin, for which effect arsenic has long had a reputation. Arsenic benefits, though only temporarily, some cases of pernicious anaemia, but liver diet has recently been shown to be much more efficacious in this disease. It is still frequently used in chronic malaria, for which purpose it was introduced by Fowler. In malaria and in diseases due to trypanosomes, it is believed to act by destroying the infective agents.

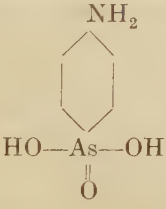
The preparation chiefly used is *Liquor Arsenicalis* or Fowler's Solution, a 1 per cent. solution of arsenious acid containing potassium carbonate, which together form potassium arsenite; some compound tincture of lavender is added which gives it a slight smell of lavender and a reddish colour. Dose 2–8 minims.

Liquor Arsenici Hydrochloricus, a 1 per cent. solution of arsenious acid and containing also some hydrochloric acid, is given in the same dose and is, unlike Fowler's Solution, compatible with most acid solutions.

Organic Compounds of Arsenic. Though in recent years there has been a decline in the medicinal use of inorganic preparations of arsenic, this has been more than compensated by the extensive employment of organic compounds of arsenic, especially in diseases due to trypanosomes and allied organisms. Arsenic was known to have some effect in syphilis and malaria,

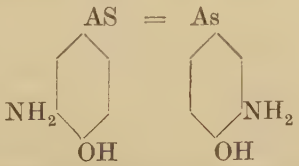
and when sleeping sickness and many other diseases were shown to be due to protozoal parasites, inorganic arsenic was tried in them. It proved, however, too poisonous to the patient to be of much value. Later an extensive series of investigations was begun on the action of organic compounds of arsenic in these diseases, to which only a brief reference can here be made.

The first important compound to be used was *atoxyl*, or the sodium salt of arsanilic acid.



This was tried with some success in sleeping sickness but was found to produce serious toxic actions, e.g. blindness. Ehrlich showed that atoxyl had no toxic action on trypanosomes *in vitro* though they disappeared from the blood when atoxyl was injected into the living animal. In atoxyl arsenic is pentavalent. Ehrlich supposed that it became actively trypanocidal in the body by being changed into trivalent arsenic. He and his colleagues investigated a long series of trivalent compounds of arsenic, which culminated in the discovery of salvarsan.

Salvarsan



or arsphenamine, U.S.P., is a compound of arsenic

with amino-benzene in which the arsenic is trivalent. It is an unstable compound which is supplied in glass ampoules from which oxygen is excluded. It is given intravenously in a large bulk of sterile saline solution. The instructions given for dissolving and administering it must be strictly adhered to, otherwise it decomposes and becomes highly toxic. Where the requisite technique has been faithfully followed, it has been given in thousands of cases of syphilis with great success and with few accidents. It does not produce blindness like atoxyl. It is superior to mercury in syphilis, especially in speed of action.

Toxic effects may occur after salvarsan injections. These effects may be due mainly to the colloidal nature of the solution and come on soon after injection—symptoms, for example, such as vomiting, diarrhoea, fall of blood-pressure, or 'anaphylactoid' symptoms such as swelling of the lips and tongue, urticaria, cyanosis, and dyspnoea. More rarely, and usually at a later period, more serious symptoms may occur which are definitely a variety of arsenical poisoning; the most important of these are cerebral symptoms (encephalitis haemorrhagica), jaundice developing into acute atrophy of the liver, and skin affections (dermatitis exfoliata).

Salvarsan is now standardized biologically (e.g. by determining the minimum fatal dose for mice) so as to ensure absence of undue primary toxicity. Since this procedure has been adopted and the necessity for scrupulous attention to every detail of its administration has been realized, serious accidents with it have become increasingly rare.

Salvarsan was found to have a curative action not only in syphilis but in several allied diseases, e.g. Frambœsia (Yaws) and Recurrent Fever.

One disadvantage of salvarsan is its instability and the technical difficulties of its administration. Other related compounds have been prepared and investigated to diminish these drawbacks. *Neosalvarsan* (or neoarsphenamine) is more stable and can be given in smaller bulk of saline and even injected intramuscularly. *Sulpharsenol* (sulpharsphenamine) can be given intramuscularly or even subcutaneously when intravenous injection is contra-indicated.

The dose of salvarsan is about 4–9 grains. As about one-third of the compound consists of arsenic, the maximum dose contains nearly three grains of arsenic, an amount which would be fatal in the form of inorganic arsenic. Neosalvarsan, which contains 20 per cent. of arsenic, is given in larger doses, 5–12 grains.

Salvarsan, as already mentioned, has proved of great value in the treatment of syphilis and other allied diseases. It failed, however, in two directions. It has little effect either in post-syphilitic nervous diseases such as locomotor ataxia and general paralysis, or in sleeping sickness. A pentavalent arsenical compound, *tryparsamide*, has recently been used with success both in general paralysis and in sleeping sickness. Like atoxyl it is liable to produce visual disturbances, but these usually disappear when the drug is discontinued.

[Two types of chemical compounds were found by Ehrlich to give promising results in the treatment of experimental trypanosomiasis in lower animals, namely, organic arsenical compounds and certain dyes. Researches on the former group have led to the introduction of salvarsan, tryparsamide, &c. Recently a substance belonging to the class of trypanocidal dyes has been introduced by the Bayer firm, called Germanin or *Bayer 205*. With this substance, promising results have been obtained in the treatment of sleeping

sickness, and it may be mentioned here though it is not an arsenical compound.]

Phosphorus

Though at one time phosphorus was regarded as an important remedy and was used in a variety of diseases, it is now seldom employed, as more certain remedies have been found for the diseases in which it was given. It therefore merits only a brief reference here.

Phosphorus is a wax-like solid which emits white fumes and may take fire spontaneously in air. It is therefore usually kept under water, in which it is only very slightly soluble. On the rare occasions in which it is given medicinally, it is prescribed in pill form or in solution in oil in a dose of about $\frac{1}{100}$ grain. Small doses given repeatedly have been shown to increase the growth of bone in young animals, and it was at one time used in rickets and other bone diseases with doubtful benefit. It has been superseded by cod-liver oil and other methods of treatment.

Phosphorus is a powerful poison; so little as 1–2 grains may be fatal in man. The symptoms of acute poisoning resemble those of arsenic. Vomiting, diarrhoea, and collapse are produced by the local irritant action on the alimentary canal. If enough be absorbed, fatty degeneration and infiltration of the liver, kidneys, and nearly all organs occurs as with arsenic, only even more pronounced.

VII

DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM: STIMULANTS

The cells of the central nervous system differ in structure, function, and evolution. It is therefore *a priori* unlikely that a drug will act on all nerve-cells quantitatively alike, and experimentally it is found that different nerve-cells vary very much in their sensitiveness to the action of drugs. Some drugs, e.g. the general anaesthetics, depress all nerve-cells more or less in the same way though in differing degrees, and display only a slight degree of selective action. For as yet unexplained reasons, some drugs influence the activities of the spinal cord rather than of the cerebrum, while with other drugs the reverse is true. Some show a very high degree of selective action within the central nervous system itself; for example, apomorphine in small doses singles out the vomiting centre almost to the exclusion of other nerve-cells. Moreover, a drug may depress some cells of the nervous system while stimulating others; for example, morphine may stimulate the cardiac vagus centre at the same moment as it depresses the respiratory centre.

The explanation, even the description, of the action of drugs on the central nervous system is therefore difficult, for we have not as yet even tentative explanations of their selective actions. There is no order of attack which is common to all drugs. Their effects have been determined by observation and experiment, but are arbitrary in so far as any reason can at present be given for their site and quality of action.

In accordance with the plan uniformly adopted in

this book, the stimulants of the central nervous system will be considered before the depressants.

Caffeine.

Caffeine is an active principle found in several plants which have come to be used in different parts of the world as stimulant beverages, e.g. tea in Asia, coffee and kola in Africa, maté in South America, and others. The effect originally attributed to these beverages, namely a sense of refreshment and wakefulness with a relief from fatigue and hunger, is borne out, as will presently be shown, by the pharmacological actions of caffeine. In view of the absence of any striking subjective sensations produced by these beverages, it is remarkable not only that these plants have been singled out in different parts of the world, but that no other plants containing considerable quantities of caffeine have been discovered by modern methods. Time and unaided observation seem to have been adequate for the discrimination of those plants which contain caffeine. Caffeine was first isolated just about a century ago from coffee, and its identity with the alkaloid in tea shown later (1838).

Action on the Central Nervous System. As is not unusual with drugs which act on the central nervous system, the action of caffeine differs somewhat in different species of animals. In all, however, the primary effect is one of stimulation. In animals with poorly developed cerebrum, like the frog, the symptoms produced by caffeine are attributable mainly to stimulation of the spinal cord; but in mammals, and especially in man, caffeine stimulates the central nervous system in the preferential order of brain, medulla, and spinal cord. The account here given will refer to the effects of caffeine on man.

Small doses of caffeine stimulate the psychical areas

of the brain. Evidence of this is seen in the increased speed and clearness of thought, in the more rapid association of ideas, and in the capacity for more prolonged intellectual effort. The feeling of mental weariness, if present, is relieved; and, as this feeling is associated with the desire for sleep, wakefulness is produced. Rather larger doses are required to stimulate the medullary centres, but especially when these centres are depressed, the stimulant action of caffeine upon them may be pronounced.

Action on the Circulation. The action of caffeine upon the circulation is somewhat complicated. The contractions of the isolated heart are quickened and very slightly augmented by caffeine, and the flow through the coronary vessels is increased. The quickening of the heart is due to a stimulant action on the pacemaker of the heart, the dilatation of the coronary vessels to a depressant action on the plain muscle of the vessels. In the intact animal these actions are modified by the stimulation of the cardio-vascular centres in the medulla. In regard to both heart and vessels, therefore, there are two opposing factors: the central stimulation of the vagus centre tends to slow the heart, whereas the peripheral action tends to quicken the heart; the central stimulation of the vasomotor centre tends to contract the arterioles, the peripheral action tends to dilate them. The net effect of caffeine on the circulation is therefore apt to be variable. In man the heart-beats are usually quickened without any marked increase in force of beat. In regard to the purely vascular effects, it must be remembered that vasoconstrictor nerves are feebly developed or absent in the heart, lungs, and central nervous system. When, therefore, the vasomotor centre is stimulated, there is little or no contraction of the arterioles of these organs. In them the peripheral

depressant action of caffeine on plain muscle is not antagonized by central stimulation. Caffeine, therefore, contracts the blood-vessels of the splanchnic area, but dilates those of the heart, lungs, and brain. While there may be little change in the systemic blood-pressure, there is a redistribution of the circulation, giving a better blood-supply to the vital organs.

Action on the Kidneys. Caffeine is a powerful diuretic, a commonly observed effect of caffeine-containing beverages. This effect is probably mainly due to an improvement in the blood-supply of the kidneys, comparable to that occurring in the heart, for, in the case of the kidneys also, the peripheral dilating action preponderates over the constriction of central origin, so that the kidney vessels are dilated while the splanchnic vessels are constricted. The blood-flow through the kidneys is increased without any reduction in the pressure, and so the secretion of urine is increased.

Action on Voluntary Muscles. The capacity of isolated voluntary muscle to perform work is increased by certain concentrations of caffeine. It is uncertain whether this action takes place in man with ordinary doses of caffeine, but it may be a factor in explaining the relief of physical fatigue and the capacity for increased muscular effort which caffeine undoubtedly produces. This effect is, however, mainly due to the stimulation of the nerve-cells, for it is these which experience fatigue before the muscles themselves are exhausted.

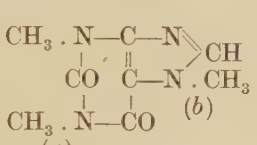
Therapeutic uses of Caffeine. The stimulant properties of tea and coffee are due to the caffeine they contain, and caffeine is of far greater importance from its general use as a stimulant in such beverages than from its purely medicinal use.

Caffeine is used as a stimulant in cases of depression of the central nervous system, for example in cases of narcotic poisoning. It is occasionally used to stimu-

late the respiratory and vasomotor centres in other conditions. As a diuretic, it has largely been supplanted by other xanthine derivatives.

It can be given in the form of the alkaloid itself (*Caffeina* 1–5 gr.), or the citrate (*Caffeinae Citras*, 2–10 gr.).

Caffeine



is a purine derivative, trimethyl-xanthine, being related, therefore, to the xanthine bodies found in the urine and tissues of animals. In the body caffeine loses its methyl groups and is excreted in the urine for the most part as dimethyl-xanthines and monomethyl-xanthines.

Of the three possible dimethyl-xanthines, two are of medicinal importance. *Theobromine*, in which the methyl group at (*a*) is replaced by H, occurs in cocoa. It has little or no stimulant action on the central nervous system, which explains the absence of this action from cocoa; it is, however, a more powerful diuretic than caffeine. Theobromine is very insoluble in water but forms a double salt with salicylate, *Theobrominae et Sodii Salicylas* (also known as Diuretin), which is freely soluble and is used as a diuretic in doses of 10–20 grains.

Theophylline or Theocine, in which the methyl group (*b*) in Caffeine is replaced by H, is isomeric with theobromine. It is the most powerful diuretic of the three, but is seldom used as it is liable to cause gastric and renal irritation.

Other Cerebral Stimulants. From the point of view of its general as well as medicinal use, caffeine is by far

the most important cerebral stimulant. Many other substances are known which stimulate the brain, but none of them resemble caffeine in producing an unmixed stimulation of the higher centres. Thus cocaine (p. 115) stimulates both sensory and motor areas, and the stimulation is often followed by depression. Atropine (p. 134) stimulates rather the motor areas, and the same is true of camphor (p. 178) and absinthe. These substances have other more important actions from the therapeutic point of view, so that they are discussed elsewhere.

Strychnine.

The seeds of **Strychnos nux vomica**, a tree indigenous to S. Asia, have for centuries been known to be poisonous. In the seventeenth century they were used in England chiefly as a poison for superfluous domestic animals. With the discovery, just over a century ago, of the active principles of the seeds (alkaloids, Strychnine and Brucine), knowledge became more precise in regard to their physiological actions, and gradually strychnine attained a position of importance as a therapeutic agent. Brucine acts qualitatively like strychnine, only is much weaker, so that there is no known qualitative difference between the actions of preparations of nux vomica and those of pure strychnine.

The most characteristic and important action of strychnine is to render the reflex centres in the central nervous system more sensitive to afferent stimuli. As its main action is on the lower and more primitive part of the central nervous system—on the reflex centres—the effects produced by it are very similar in all vertebrates, whereas drugs which act on the cerebral cortex may produce very dissimilar effects in different species of vertebrates. In medicinal doses strychnine stimu-

lates the spinal cord but not the brain, caffeine stimulates the brain but not the cord: both alkaloids have a less pronounced effect on the medullary centres.

Small doses of strychnine, such as are used therapeutically, do not alter the path of a reflex: they merely exaggerate the normal response. Larger doses cause reflex impulses to spread through the central nervous system with increasing facility, so that the normal responses may be altered. An afferent impulse, which would normally be reflected through one set of motor neurons, may now induce an ever-widening discharge of motor impulses until, with poisonous doses of strychnine, generalized convulsive movements of voluntary muscle are produced.

Owing to the nature of their production, strychnine convulsions often display a typical character. When a muscle contracts, its antagonistic muscle is not inhibited; all voluntary muscles contract more or less simultaneously, and the stronger overcome the weaker. Thus, for example, the more powerful extensor muscles of the back overcome the flexors, so that in strychnine convulsions the vertebral column may be arched with the concavity backwards—so-called opisthotonus. Convulsions are usually succeeded by intervals of complete relaxation of muscles, until the nervous system recovers from exhaustion, whereupon convulsions recur. Consciousness is retained during the convulsions, and intense pain is felt from the violent contracting or stretching of muscles. Death occurs usually from spasmodic fixation of the respiratory muscles or from exhaustion of the central nervous system, especially the respiratory centre. Strychnine convulsions are singular in the ease with which they are provoked by slight afferent stimuli, e.g. a current of air or a sudden noise.

Apart from a stimulant action on reflex centres,

strychnine has no important action in medicinal doses. It temporarily increases the acuity of the special senses, especially of sight, leading to an increase in the field, and in the acuity, of vision.

Therapeutic uses of Strychnine. Strychnine can be used whenever it is desirable to increase reflex excitability. It is useful in some kinds of paralysis, e.g. due to lead or diphtheria toxin, where it may improve the tone and nutrition of the paralysed muscles. It is sometimes used as a respiratory and circulatory stimulant, from its stimulating the respiratory and vasomotor centres. It has no direct effect on heart-muscle.

Strychnine is usually given in the form of a soluble salt, by mouth or hypodermically (*Strychninae Sulphas* or *Nitras*, U.S.P., and *Strychninae Hydrochloridum*, B.P.) in a dose of $\frac{1}{60}$–$\frac{1}{15}$ grain or more. *Liquor Strychninae Hydrochloridi* (B.P.), a 1 per cent. solution given in doses of 2–8 minims, is a convenient form in which to prescribe it in mixtures. Preparations of Nux Vomica seeds are now less frequently used, but the *Tinctura Nucis Vomicae* (5–15 min.) is still often prescribed.

VIII

DEPRESSANTS OF THE CENTRAL NERVOUS SYSTEM

Alcohol and the General Anaesthetics

Alcohol is of medicinal importance from several points of view. It is widely used as a solvent for the active principles of drugs. It is in common use as an external application, chiefly as an antiseptic. When taken internally, its actions have a twofold interest, as a basis for possible therapeutic uses of alcohol, and as an explanation, justification, or condemnation of the use of alcoholic beverages.

Of the series of alcohols, ethyl alcohol is from these points of view by far the most important, and therefore will be considered first.

Local Actions of Ethyl Alcohol. Strong alcohol applied to the skin is irritating, especially if evaporation be prevented. It partly precipitates proteins and tends to harden the skin, and is used for this purpose to prevent bed-sores in people who are confined to bed with exhausting illnesses. It is a valuable antiseptic for the skin, especially in preparing the skin for operation. It is important to remember that the antiseptic activity of alcohol is not proportional to its concentration. The optimum concentration for antiseptic action is about 70 per cent. Both above and below that concentration it becomes less antiseptic. To a mucous membrane, it is, as one would anticipate, more irritant than to the skin. In concentration it has a burning taste and irritates the mouth and alimentary canal, and continued use of strong alcoholic beverages tend to produce chronic gastritis. In concentra-

tions below about 20 per cent., alcohol psychically stimulates the gastric secretions and also directly stimulates them.

Absorption and Fate of Alcohol. This naturally depends to some extent upon the initial dilution of alcohol, upon the absolute amount of it and its relation to food, so that the following statements represent rather an average of truth. Alcohol is rapidly and completely absorbed from the stomach and small intestine. It is one of the very few substances to be absorbed from the stomach. It begins to appear in the blood in a very few minutes, and attains a maximum concentration there in from 1 to 2 hours. It disappears from the blood with surprising slowness, not completely even in 18 hours. Its disappearance is due almost entirely to oxidation of it in the tissues, only small quantities of it appearing in the urine and breath. On account of the slow rate of its oxidation, the ultimate maximum concentration of it in the blood is nearly the same when a quantity of alcohol is taken in divided doses (so long as the interval is not more than 2 hours) as when it is taken in one dose, though of course the attainment of that maximum takes longer. A given quantity of alcohol is absorbed more slowly and attains a lower maximum when taken in a dilute solution than when taken more concentrated.

Alcohol as a Food. The oxidation of alcohol must yield energy, and alcohol is therefore a 'food', but there are some important differences between it and other foods. In the first place the rate of alcoholic combustion, and therefore the equivalent liberation of energy, is almost independent of the concentration in the blood. About 10 c.c. of absolute alcohol per hour can be oxidized by an adult man, but not more, however high the concentration in the blood. Within the limits of this rate of combustion it can replace carbo-

hydrates and fats, and supply about one-third of the total energy requirements of the body. In the second place (unless when present in low concentrations in the tissues), it does not undergo combustion at a more rapid rate during exercise than during rest. The liberation of energy derived from its combustion is therefore not adjustable to the energy requirements of the body. Lastly, if more is taken than can be oxidized, the concentration rises in the blood, and the toxic actions of alcohol make themselves manifest.

Besides being an expensive food, it is therefore a food which is difficult to regulate and which can fulfil only a limited function. It has one merit. It is rapidly absorbed without requiring any digestion, and, if sufficiently diluted, does not interfere with the organs or processes of digestion.

Action on the Circulation. Alcohol, usually in the form of whisky or brandy, i.e. fairly concentrated, is often used as a stimulant in fainting or acute circulatory failure. Since little (or, as most people think, no) stimulation of the heart is produced when alcohol is perfused through an isolated heart, its main effect here seems to be a reflex stimulation of the circulation produced by the irritation of the mouth and stomach. Even moderate doses of alcohol produce a dilatation of skin-vessels, a very general effect of hypnotic drugs. Owing to this effect, as well as from its depressing the central nervous system, alcohol tends to lower the body temperature.

Action on the Central Nervous System. By far the most important action of alcohol is its action on the nervous system. It is this action which is mainly responsible for the use and abuse of alcoholic beverages, and which has led to the prolonged dispute as to the advisability of their prohibition. Into the minor details of this action it is impossible to enter here. It is

now generally conceded by those who have carefully studied the subject that alcohol is a depressant of the central nervous system, and that only under very exceptional circumstances can it be said to have any stimulant action at all. This is true whatever the dose or dilution of it.

The depressant action of alcohol is exerted chiefly on the brain, and first affects those regions or functions of the brain which are evolutionally the last to be developed. They involve those mental qualities which especially distinguish man from the lower animals, and the adult man from the child; the faculties of judgement, concentration, self-criticism, the power of 'calculating the odds', the faculty of speech, and the ability to maintain steady progression in the erect posture. As the result of depression of the higher centres, the influence of which on the lower centres is largely of an inhibitory or controlling nature, a person becomes, under the influence of alcohol, more childlike, more emotional, more reflex. Alcohol tends to induce a feeling of well-being and of freedom from care, and a subjective sensation of increased mental and physical capacity. This effect is largely due to the depression of the higher centres, with the consequent subjection of the sense of responsibility and of self-criticism. For, where mental processes or physical capacity are capable of measurement, they are found to be not enhanced but deteriorated by alcohol. A great variety of such experiments have been made, e.g. on reflex time; on association; on work involving concentration and co-ordination of muscles, such as shooting; on work involving memory, attention, and skilled muscular movements, such as typing; on endurance in marching, and so on,—all of which have led to the general conclusion that alcohol lessens the acuity of mental processes and retards the execution of skilled movements.

Very large doses of alcohol depress the whole central nervous system, eventually producing paralysis of reflexes and coma, and, if the dose be fatal, death mainly from paralysis of the respiratory centre. In these doses it resembles in its effects the general anaesthetics.

Therapeutic uses of Alcohol.

In an attempt to estimate the therapeutic value of alcohol, it is impossible to be brief without being dogmatic. Alcohol has so long been used in the form of alcoholic beverages, as well as for medicinal purposes, that the whole question is obscured by traditional beliefs. However, even if knowledge be confined to laboratories, wisdom is the general heritage of mankind ; and it is fair to say that recent exact research has confirmed many of the traditional opinions in regard to the effects of alcohol. It is convenient to take the therapeutic uses in the order in which the pharmacological actions have been considered.

As a Stimulant of Digestion. It is a general belief that the use of an alcoholic beverage may, under certain circumstances, be an aid to digestion. The belief is well-founded. This effect is due to three factors, the relative prominence of which varies in different individuals and under different circumstances. There is, firstly, the psychical effect on appetite and digestion. If a glass of beer or of wine appeals to the palate, it will reflexly stimulate appetite and digestion. Secondly, when alcohol enters the stomach it may directly stimulate the gastric glands. This is more likely to happen if the alcohol be above 10 per cent., e.g. of the strength of wines rather than of beers (below 4 per cent.). In the third place, the depressant action of alcohol on the brain, which tends to produce a sense of freedom from care, may improve appetite and

digestion in cases where anxiety or mental abstraction is likely to interfere with digestion. On the other hand, it is equally true that persons of normal health of mind and body do not require any such artificial stimulus to digestion. In cases of ill health, however, especially when accompanied by loss of weight, this action of alcohol is often beneficial.

As a Food. The advantages and disadvantages of alcohol as a food have already been considered. It will be obvious that, for people in normal health and receiving a sufficient diet, alcohol is a quite unnecessary food. Indeed the probability is that it will be deleterious, because the addition of alcohol to the diet is seldom accompanied by an equivalent diminution of other foods, so that a person who regularly uses alcohol even in moderate amounts is liable to lay down a useless, and sometimes an embarrassing, amount of fat. During some acute diseases, however, and during convalescence, the mere food-value of alcohol may be considerable. It ought to be given in small quantities frequently repeated, so as to allow of its being oxidized sufficiently completely to prevent an intoxicant concentration in the blood.

As a Stimulant to the Circulation. As already pointed out, alcohol has no direct effect on the contractions of the heart, comparable for example to that of adrenaline or of digitalis. The reflex stimulation which it produces resembles rather that which can be provoked by other irritants of the mouth and stomach, and the effect is neither powerful nor lasting. Moderate doses of alcohol have little effect on the blood-pressure. The dilatation of the skin-vessels which it produces gives rise to a feeling of warmth, a sensation which is dependent mainly upon the blood-supply to the skin. This has led to the use of alcohol in preventing the effects of 'chill'. Chill seems to be due not so much to mere ex-

posure as to unequal exposure of the surface of the body to cold. Alcohol tends to produce a more equal distribution of blood in the skin, and does in certain circumstances prevent the effects of chill. But as the result of the dilatation of the superficial vessels as well as from its depressant action on the nervous system, alcohol tends to lower the body temperature. The advisability of the use of alcohol in preventing chill will depend, therefore, upon a variety of circumstances; e.g. the age and robustness of the person, the intensity and duration of the exposure. Man can hardly have survived throughout the ages without having a mechanism competent to deal with any ordinary exposure to cold. It is near the truth to say that, if necessary at all, alcohol should be given only after exposure, and when, in warm surroundings, its action in lowering temperature would be negligible.

As a Cerebral Sedative. Probably the majority of people who take any form of alcoholic beverage take it for its depressant action on the brain. If alcohol possessed all its other actions but lacked this, there would be no alcohol problem. The control over the emotions and the sometimes unnecessary control over the imagination, which are acquisitions largely of adult life, are temporarily suspended by alcohol, and therefore freer play is given to the emotional side of mind. As De Quincey conversely puts it, 'Sobriety disguises a man'. The chief attraction of alcohol is that it blunts the edge of the critical faculties, which indeed is sometimes too sharp for the ordinary affairs of life.

The sedative action of alcohol is sometimes of medicinal value in facilitating sleep. It is a safe and valuable hypnotic, for example, in young children, and a 'night-cap' is not always detrimental at the other extreme of life.

The use of alcohol is not without well-known

dangers. Frequent use gives rise to a habit, which it may be difficult to interrupt. Over-indulgence is disastrous. No strength of will can prevent the physiological effects of alcohol on the tissues, or the deteriorating effect of over-indulgence on the brain-cells themselves.

It may seem at first sight rather a paradox that men should have come to employ, for their relief, substances having opposite actions, as exemplified on the one hand by caffeine which stimulates the brain, and on the other hand by alcohol and opium which depress the brain. But the end achieved by members of each group is different. Caffeine, by stimulating the higher functions of the brain, produces a sense of well-being due to increased capacity for mental and physical work; alcohol or opium, by depressing these functions, produces a sense of well-being due to relief from mental or physical pain. In countries where both are available, a person may elect at one time to take a beverage containing caffeine, at another time one containing alcohol; or, of course, he may disdain the use of either or both.

Other Alcohols.

The acute toxicity of the alcohols, as determined by the minimum fatal single dose, increases with the size of the molecule, so that methyl, ethyl, propyl, butyl, and amyl alcohols show a progressive increase in toxicity. The alcohols higher than ethyl alcohol are of little medicinal importance. **Methyl alcohol**, however, is important from the poisonous effects it may produce when used as an adulterant of alcoholic beverages or as a solvent, &c., in the arts. While the minimum lethal dose of methyl alcohol is slightly less than that of ethyl alcohol, the former is far more poisonous than the latter, judged from any other point of view. It is more slowly destroyed in the body,

so that intoxication with it is more prolonged and it is more likely to be cumulative. It also may produce serious symptoms which practically never occur with ethyl alcohol. Chief among these is optic neuritis, leading to blindness. The amount required to produce this varies very much in different individuals, but as little as 10 c.c. is alleged to have caused blindness. The adulteration of a beverage with methyl alcohol, therefore, constitutes a very serious danger.

General Anaesthetics

It is interesting to remember that the applied use of general anaesthetics began only about eighty years ago. Forty years earlier Davy had noticed that inhalation of nitrous oxide produced a loss of sensation of pain and had suggested that it might be used for this purpose in surgical operations, but it was left for Wells, an American dentist, to rediscover and apply this action of nitrous oxide to the induction of general anaesthesia in 1842.

Long seems to have been the first to use ether as a general anaesthetic in the same year, and Simpson the first similarly to employ chloroform five years later. Those three general anaesthetics, which have retained a pride of place ever since, were therefore all launched upon an expectant world in the space of five years, 1842 to 1847; and though some attempts were made to oppose their introduction (on the grounds that the abolition of pain was an interference with the prerogative of God), the practice of general anaesthesia rapidly spread until it is now difficult to realize that we are separated only by the span of a human life from the days when major operations were performed with the attendant pain unrelieved.

Though in the original quest for a suitable general anaesthetic the discovery and adoption of volatile

substances which could be administered by inhalation were largely a matter of accident, experience soon revealed certain great advantages attaching to inhalation, as compared with other methods of administration, for this purpose. The lung has a very large surface, specially adapted for rapid absorption and elimination of gases. When a volatile substance is given by inhalation, its physiological action can therefore be produced rapidly; the amount given is under continuous control, if an excessive amount has been given, the unabsorbed anaesthetic can easily be removed, and, provided that circulation and respiration continue, the anaesthetic is rapidly eliminated by the lungs when its administration is discontinued. Though general anaesthesia can be produced by oral administration of a suitable substance, induction of such anaesthesia is usually slower, its maintenance at an optimum level more difficult to ensure, and, if an excessive dose be given, removal of this excess is less easy and less rapid.

Ether.

Ether is a colourless, mobile liquid, having a characteristic odour and a burning taste. It is highly volatile and inflammable; specific gravity about 0·7; boiling-point about 35° C.; soluble in about twelve parts its volume of water at 25° C. It is an oxide of ethyl $(C_2H_5)_2O$; and is therefore closely related chemically to ethyl alcohol, C_2H_5OH. Corresponding with this similarity in chemical constitution, one would anticipate that ether and ethyl alcohol would resemble one another also in their pharmacological actions; and this in fact they do. The differences in their action and uses, though these are of great practical importance, are due very largely to differences in their physical properties. Ether is, for instance, much

more volatile than ethyl alcohol; so much so that it can be given by inhalation, because a sufficient concentration in air can be obtained to produce rapidly the full physiological actions of it. This is not possible with alcohol. Another important difference between the two is that, whereas alcohol is almost completely destroyed in the body, ether is eliminated by the lungs—very little, if any, of it being oxidized.

When given by mouth, ether can produce a kind of intoxication which is very similar to alcoholic intoxication, but its great medicinal importance rests upon its use as a general anaesthetic when given by inhalation. Like alcohol, it depresses the central nervous system, and the possibility of the employment of a substance as a general anaesthetic depends upon selective action on the central nervous system. In order that a surgical operation may be painlessly and delicately performed, not only must the sensation of pain or even consciousness be suspended, but reflex movements must also be eliminated. These conditions can be attained by paralysis of the brain and spinal cord. But a substance could not be used as a general anaesthetic if the medullary centres were simultaneously paralysed, as in that case respiratory and circulatory failure would occur at the same time as abolition of pain and reflex movement. Fortunately the vital centres are, of the whole central nervous system, least susceptible to the action of ether. Consequently the aim in giving ether as an anaesthetic is to get into the blood a sufficient concentration to suspend the functions of the brain and cord, but to stop short of that higher concentration which would paralyse the respiratory and cardiovascular centres in the medulla. This sequence of attack on the central nervous system is true of all the general anaesthetics, but it is to be remembered that it is not an inevitable sequence, because substances are

known which paralyse the functions of the vital centres before those of the brain or spinal cord. General anaesthesia is produced only when ether reaches a certain concentration in the blood. Usually this takes several minutes, during which time the concentration is gradually rising, and the symptoms correspondingly changing. For convenience in comparing anaesthetics, one may consider (1) the local action of the anaesthetic, (2) the induction stage, and (3) the anaesthetic stage. Details of administration of anaesthetics can best be learnt practically. To induce anaesthesia, ether has to be inhaled in a concentration of about 6 per cent. (by volume) in air. Less is required to maintain anaesthesia once it is induced. This vapour is irritant, and produces the usual effects of irritation of the upper air-passages, e.g. salivation, coughing, increased discharge from the respiratory glands. During the induction stage, the general symptoms resemble first those of deepening alcoholic intoxication. The senses become less acute, and there is vertigo with loss of muscular control. Usually there is a period of excitement marked by tremor, struggling, or shouting, with imperfect consciousness. These symptoms are generally supposed to be due to the paralysis of the higher and inhibitory centres of the brain. As the anaesthetic is continued, depression spreads down the central nervous system, sensations, including that of pain, are abolished, the muscles relax, and eventually the reflexes disappear, and the patient is unconscious and motionless apart from the movements of respiration. At this time respiration is slower and shallower than normal, but the circulation is little affected. If ether is pushed beyond this stage, the respiratory centre is paralysed, but the blood-pressure is usually fairly high and the heart continues beating for some time after respiratory movements cease.

Chloroform,

$CHCl_3$, is a clear colourless mobile liquid, having a characteristic odour and a burning sweetish taste. It is soluble in about 200 parts of water; specific gravity about 1·5, boiling-point about 61° C. One gramme of chloroform, when evaporated, yields about 200 c.c. of vapour at 15° C.

Chloroform resembles ether as a general anaesthetic, but is a more powerful depressant of the central nervous system. This is shown by the fact that, to produce anaesthesia, the concentration of ether in the blood has to be 3 to 6 times as high as that of chloroform. Correspondingly, the concentration in air necessary to produce anaesthesia has to be much less with chloroform, and thus the latter irritates the air-passages less. This is one great advantage of chloroform over ether; the latter may occasionally produce post-operative bronchitis or even pneumonia, but this is very rare with chloroform.

The induction stage tends to be less prolonged, and the excitement less marked with chloroform than with ether, and the former is more pleasant to take. These differences are to the advantage of chloroform, but they are, for most operations, outweighed by the superior safety of ether. Statistics vary with the skill of the anaesthetist, but they tend to show that, in an equal and large number of administrations, there are three times as many deaths from chloroform as from ether. Death from chloroform may arise in three different ways.

1. Early in its administration, indeed often before the patient is anaesthetized, the heart may suddenly stop. This may sometimes be due to stoppage of the heart from stimulation of the vagus centre, but in man is usually due to fibrillation of the ventricles. When

the ventricles fibrillate the pumping force of the heart ceases immediately. The gravity of this condition consists in its occurring with little or no warning, and in the great difficulty of restarting the heart.

2. Death may occur at any time during the administration merely from too high a concentration in the blood. When this happens, the respiration fails first, but at this time the circulation is also enfeebled, because the concentration which arrests the respiration depresses both the vasomotor centre and the heart-muscle. Recovery by artificial respiration is therefore less certain than in the case of respiratory failure with ether.

3. Especially in young subjects and after prolonged abdominal operations, chloroform may give rise to destructive changes in the liver. In these cases, after recovery from the anaesthetic, the patient may develop vomiting, delirium, and a rapidly fatal coma. This type of 'delayed' poisoning usually begins one or two days after anaesthesia and does not occur with ether.

Generally speaking, ether is now used more frequently than chloroform owing to its superior safety, but in certain cases, e.g. in alcoholics who are resistant to ether, or in patients with lung diseases in whom bronchial irritation must be avoided, chloroform is sometimes preferred.

Ethyl Chloride (C_2H_5Cl) is a very volatile liquid which boils at 12° C. It has been used as a general anaesthetic, given by inhalation. It is kept as a liquid in sealed tubes, the vapour volatilized from which is inhaled through a mask. It induces anaesthesia quickly, but prolonged anaesthesia is difficult to maintain with safety. In toxic action it comes, as one might expect from its chemical constitution, somewhere between ether and chloroform.

Ethyl chloride may also be used as a local anaesthetic, for which purpose it is sprayed in a fine jet on the surface. It causes loss of sensation largely by the cooling of the tissues caused by its rapid evaporation.

Nitrous Oxide (N_2O) is a colourless gas which for convenience of use is stored under pressure in metal cylinders. When pure nitrous oxide is inhaled, it rapidly produces unconsciousness, usually without any marked stage of excitement. When a mixture of air and nitrous oxide, containing anything less than 80 per cent. of the latter, is inhaled, it produces a kind of intoxication, often accompanied by laughter, whence the name 'laughing gas'; but in this case no complete anaesthesia is produced.

Nitrous oxide is not decomposed in the body, and its contained oxygen is useless for the purpose of respiration. Obviously, therefore, if it is inhaled pure, it will produce asphyxia. The technique of its administration is therefore different from that of ether or chloroform; for if it is to be used as a general anaesthetic, the problem must be solved of how to give a sufficient concentration of it to produce general anaesthesia without producing a dangerous degree of asphyxia. This problem has been solved in two chief ways, corresponding to the two common methods of employing nitrous oxide as an anaesthetic.

1. For very short operations, for example the removal of teeth, the administration of a few inhalations of almost pure nitrous oxide can produce general anaesthesia. In order that the patient should receive the gas undiluted, a special apparatus is necessary, involving a mask fitting closely over the face.

The chief advantages of this method of producing general anaesthesia are as follows: Anaesthesia is rapidly produced, and no previous special preparation of the patient is absolutely necessary. The patient

can be anaesthetized in the sitting position. There are no important after-effects, the patient being normal, as far as the anaesthetic is concerned, in a few minutes. Lastly, the method is the safest of all methods of producing general anaesthesia. Against these weighty advantages is the great disadvantage of the shortness of the anaesthetic, which lasts only from 30 to 60 seconds, more prolonged anaesthesia being impossible owing to the onset of asphyxia.

2. For more prolonged anaesthesia, nitrous oxide can be given (with the help of a specially designed apparatus) mixed with pure oxygen. A mixture of 90 per cent. of nitrous oxide and 10 per cent. of air will contain only 2 per cent. of oxygen. This is insufficient to prevent anoxaemia. A mixture of 90 per cent. of nitrous oxide and 10 per cent. of oxygen will, however, give a sufficiently high concentration of the former to act as an anaesthetic and enough oxygen to prevent serious anoxaemia.

Partial asphyxia by itself acts to some extent as an anaesthetic, but nitrous oxide also has a direct depressant action on the central nervous system, as is shown by the fact that a mixture of 90 per cent. *nitrogen* with 10 per cent. of oxygen has no anaesthetic action comparable to a corresponding mixture of nitrous oxide, though the anoxic qualities of both are similar.

Ethylene ($CH_2 = CH_2$) has come into use as a general anaesthetic within the last five years, and has been used successfully for all types of surgical operations. It is a gas at ordinary temperatures, and is supplied, compressed, in metal cylinders. It is generally given as a mixture of 90 per cent. ethylene with 10 per cent. oxygen. Such a mixture rapidly produces general surgical anaesthesia with little or no cyanosis. It seems to be usually as effective as ether, and superior to it in absence of after-effects.

The mixture of ethylene with oxygen is highly explosive, so that scrupulous care must be taken to avoid the possibility of its coming in contact with an open flame, electric spark, or cautery.

IX

DEPRESSANTS OF THE CENTRAL NERVOUS SYSTEM: HYPNOTICS

As has already been pointed out, chloroform produces, at the commencement of induction of general anaesthesia, a condition of drowsiness, due to depression of the higher centres of the brain. At this stage there is no marked impairment of motility or alleviation of pain. Chloroform might be used therefore merely for the induction of sleep in people suffering from insomnia. It would, however, be difficult and even dangerous to administer for this purpose, and, moreover, its action would be too evanescent. Merely for inducing sleep it would clearly be an advantage to have a substance which could be given by mouth and which would produce a slighter but more enduring effect. About twenty years after the introduction of chloroform anaesthesia (1868), Liebreich discovered that a substance, chloral hydrate, possessed these properties, and it was the first of a long series of compounds to be tried for use as hypnotics, only a few of which can be mentioned here.

Prior to the discovery of the hypnotic action of chloral, only such naturally-occurring substances as opium had been used to produce sleep. The members of the group first to be considered are often called artificial hypnotics, because they are manufactured in the laboratory, in contradistinction to such substances as opium which are derived from plants. The words hypnotic, soporific, and narcotic are all used to designate drugs employed to induce sleep.

Chloral Hydrate, $CCl_3CH(OH)_2$, is a chlorinated derivative of ethyl alcohol. It is a colourless, crystal-

line substance, soluble in water, with a burning taste and pungent fruity odour.

It has an irritant action which is displayed even on the unbroken skin and more conspicuously on mucous membranes; consequently it must be given well diluted, otherwise it may cause vomiting. Owing to its extreme solubility, it is rapidly absorbed when given by mouth, and exercises its main action on the central system, which it depresses. Given by mouth in a dose of 10 to 20 grains, it produces within half an hour a condition of drowsiness which, under favourable conditions, will induce sleep. This sleep is hardly distinguishable from natural sleep and usually passes off in 6 to 8 hours, by which time most of the chloral has been excreted.

If the dose be increased (e.g. 50 grains), the sleep produced is deeper, the patient more difficult to arouse, and the sensation of pain is dulled; the respiration is slower, and the pulse may be weaker. With still larger doses, complete anaesthesia with abolition of reflexes is produced—a condition almost identical with chloroform anaesthesia. It would be difficult to use it as a general anaesthetic in man, however, because the anaesthetic dose is too near to the dose which also paralyses the respiratory centre.

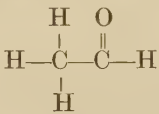
Chloral depresses the central nervous system very much in the same order as the general anaesthetics; that is, first the brain, then the spinal cord, and lastly the medullary centres. Medicinal doses stop short of the last action, and produce a dulling of the sensory activities of the brain and spinal cord. It is used therapeutically in cases of insomnia and nervous excitability.

In large doses chloral depresses the heart-muscle as well as the respiratory and vasomotor centres, but there is no danger of this happening with medicinal

doses. Chloral is therefore an excellent and reliable hypnotic.

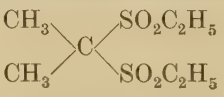
In the body it is mostly reduced to trichlorethyl alcohol which combines with glycuronic acid, and the resulting combination, called urochloralic acid, together with some unchanged chloral, is excreted in the urine.

Paraldehyde $(CH_3 . COH)_3$ is a polymer of ethyl aldehyde



It bears a considerable resemblance chemically to chloral but contains no chlorine. It differs in this respect from chloral in the same way as ether differs from chloroform, and there is a corresponding difference in the pharmacological actions of the two pairs of substances. Paraldehyde is a mobile liquid, soluble 1 in 10 of water; with a hot burning taste and persistent, unpleasant, odour. It was introduced as a hypnotic in 1882. It acts very like chloral, and produces sleep in about 15 minutes. Its chief advantage is its safety and that, owing to its disagreeable taste and smell, it is less liable than other hypnotics to induce habit-formation. Its chief disadvantage is that it is disagreeable to take and, owing to its slight solubility, rather difficult to dispense elegantly. The usual dose is, B.P., $\frac{1}{2}$–2 fl. dr. (2–8 c.c.); U.S.P., 30 mins. (2 c.c.). It may be prescribed in iced water, brandy and water, or in capsules.

Sulphonal, B.P., Sulphonmethanum, U.S.P.,

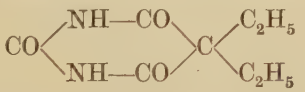


was introduced as a hypnotic in 1888. It is an insoluble, tasteless, crystalline powder, very slightly

(about 1 in 400) soluble in cold water, 1 in 15 in boiling water. Owing to its insolubility, it is slowly absorbed, and this is a serious disadvantage, because the onset of sleep is delayed for a varying time, e.g. 1 to 5 hours. It is therefore difficult to time its administration, and moreover, owing to its slow excretion, it is apt to produce drowsiness and confusion on the following day. Especially in anaemic women, it may produce haematoporphyrinuria and it is apt to be cumulative. It has no great merits to outweigh these disadvantages and is now little used. Dose, B.P., 10–30 grains (0·6–2 grammes); U.S.P., 12 grains (0·75 gramme), as a powder.

Trional (Methylsulphonal, B.P.; Sulphonethylmethanum, U.S.P.) is similar in structure to sulphonal, except that one CH_3 group in the latter is replaced by C_2H_5. It is rather more soluble (1 in 200) than sulphonal, and prompter in action, but otherwise has the same disadvantages.

Veronal (Barbitonum, B.P.; Barbitalum, U.S.P.) has been in use as a hypnotic for about a quarter of a century. It is a compound of urea, diethyl barbituric acid.



It is a white crystalline powder, with a slight bitter taste, soluble 1 in 130 in cold, 1 in 13 in boiling water. In medicinal doses it has little action except on the central nervous system, producing sleep in ½ to 1 hour, with usually little after-effects. It is widely used as a hypnotic. Acute poisoning, with death from collapse and coma, is not uncommon, but only from larger than medicinal doses. Veronal is prone to induce habit-formation, in connexion with which chronic poisoning is not infrequently seen. This is characterized by

impaired mental ability, diplopia, ataxia, and occasionally cyanosis and an erythematous rash.

The dose of veronal is 5–8 grains (0·3–0·5 gramme); usually prescribed in powder or tablets. The sodium salt of it, Medinal (Barbitalum Solubile, U.S.P.), is freely soluble in water and acts quicker.

Luminal (Phenobarbitalum, U.S.P.) is similar to barbitone but that one ethyl group is replaced by a phenyl group, whence its official name. It is a white crystalline powder, soluble only 1 in 1,000 in cold water. It is a more powerful hypnotic than veronal, and more valuable for subduing motor excitability. It is used, for example, in delirium tremens and especially in epilepsy. The U.S.P. dose of $\frac{1}{2}$ grain (0·03 gramme) is often exceeded, but $2\frac{1}{2}$ grains is about the maximum. The sodium salt of luminal (Sodium Phenobarbitalum, U.S.P.), dose $1\frac{1}{2}$–5 grains (0·1 to 0·3 gramme), is freely soluble and is sometimes given hypodermically where a quick action is desired, e.g. in status epilepticus.

Bromides.

Among simple salts, bromides occupy a peculiar position on account of their depressant action on the central nervous system. To most tissues, except nerve-cells, it seems to be indifferent whether they have chlorides or bromides in their environment. The actions to be described are due to the bromide ion and are therefore produced by any substance which liberates this in the blood. The potassium salt is most frequently used medicinally.

Bromides are rapidly absorbed from the intestine, and in sufficient doses induce symptoms of impaired mental activity, lethargy, diminished reflex excitability, and drowsiness. Pain sensation is hardly affected, but the excitability of the motor cortex is reduced. Very large doses produce inco-ordination of movement

and stupor. The chief action of bromides is therefore to diminish the excitability of the motor areas of the brain. As they do not usually affect other tissues of the body, bromides may be given continuously for long periods if necessary, to produce a lasting depression of the central nervous system. They are used especially in epilepsy, in which disease they usually reduce the number of fits but have to be given for months or even years in daily amounts of 60 grains or more. Given in single or a few repeated doses of 10 to 30 grains, bromides are used in the treatment of insomnia due to mental worry, or in order to control cerebral excitement.

After absorption, bromides are distributed in the body exactly like chlorides, and even the kidney does not differentiate between them but excretes them in the urine in the same proportions as they occur in the blood. If a single dose of bromide is given, some of it therefore appears quickly in the urine, but it may take weeks before the whole of it is eliminated. Consequently bromides accumulate in the blood if given continuously, replacing chlorides in the blood to an extent which depends upon the relative amounts of each ingested. Such an increase of bromides in the tissues is necessary in the treatment of epilepsy. Sometimes, as the result of this, undesirable effects of bromides ('Bromism') occur. Of these the most prominent are skin eruptions, disturbances of digestion, and mental impairment.

Opium Alkaloids

Opium is the dried juice of the white poppy, *Papaver somniferum*, which is cultivated chiefly in S. Asia, for the purpose of supplying this juice. Opium has been used as a narcotic from very early times. It surpasses all known drugs in relieving pain in doses which do not conspicuously impair other functions of the brain, and

this property, together with others only less important, make it one of the most valuable of remedies.

Opium owes its pharmacological actions to the alkaloids contained in it, of which there are many. The most important of these is morphine, which forms about 10 per cent. of opium. Morphine was first isolated from opium in 1814, and has gradually supplanted opium for many purposes. Morphine has the advantages over opium that it has an unvarying composition and, in the form of a salt, can be injected hypodermically. The actions of opium are due mainly to morphine, but the presence of other alkaloids which do not act precisely like morphine makes the actions of opium not identical with those of morphine. It will be convenient therefore first to consider the actions of morphine and subsequently the more complex actions of opium.

Morphine,

though acting mainly as a depressant, does not affect the functions of the central nervous system quite in the same way as the general anaesthetics and hypnotics, but displays a more marked selective action than they do. The medicinal dose of morphine is from $\frac{1}{8}$–$\frac{1}{2}$ grain. The smaller of these doses produces a feeling of drowsiness with disinclination for movement, a distinct lessening of the sensation of pain if present, and some slowing of the respiration. If the environmental conditions are conducive to it, the patient may pass into a light sleep.

In a dose of $\frac{1}{4}$ to $\frac{1}{2}$ grain, morphine produces deeper sleep from which the patient can be temporarily aroused. The reflexes are weakened and the senses less acute. The respiration is distinctly slower, the skin somewhat congested and the pupils are contracted. With still larger doses the pupils become still smaller,

coma deepens, and, in fatal cases, death occurs from arrest of respiration.

These symptoms point to a depression of the central nervous system beginning with the higher centres. The action in some ways resembles that of alcohol. The loss of judgement, combined with exaltation of imagination and relief of pain and discomfort, are largely responsible for the pleasure which some people derive from morphine and for the seductive habit which it may create in them.

Therapeutic uses. The chief therapeutic value of morphine depends upon its power to relieve pain, physical discomfort, and mental anxiety. A dose which will relieve pain may leave intelligence but little impaired. A constant pain is relieved better than sudden sharp pain. It has therefore a wide use for the relief of pain, sleeplessness due to pain, or restlessness and anxiety due to haemorrhage, &c. Owing to the serious danger of habit-formation, it is specially indicated only in acute disease of short duration or in pain of terminal diseases.

Morphine depresses the respiratory centre. It is rarely necessary to do this in the treatment of disease, but it is often advantageous to diminish the excitability of the allied cough centre, which morphine likewise depresses. It is widely used for this action in checking useless cough (i.e. cough which is not fulfilling its physiological function of clearing the air-passages) when that is interfering seriously with the well-being or sleep of the patient.

Morphine is also much used for the relief of severe colic and abdominal pain. It effects this partly by its central analgesic action, but in some conditions it also quietens intestinal movements. It therefore tends to produce constipation, and is sometimes used in the treatment of diarrhoea.

Morphine is excreted partly by the kidney and partly by the mucous membrane of the alimentary canal. When it is taken habitually, a high degree of tolerance may be acquired to it, so much so that an *habitué* may take with impunity quantities which would kill several people unaccustomed to it. Various reasons have been given to explain this tolerance, e.g. increased destruction of the alkaloid in the body or more complete elimination, but in addition to this the cells of the central nervous system become less sensitive to it.

Of the many other alkaloids found in opium, only one, *codeine*, is as yet official. It resembles morphine in action, but is weaker and less certain. It is chiefly used in the form of Codeinae Phosphas ($\frac{1}{4}$–1 gr.) in the treatment of cough. It has the merit of rarely, if ever, inducing habit-formation.

Papaverine and *Narcotine*, two other unofficial alkaloids found in opium, differ from morphine in chemical constitution and to some extent in pharmacological action. Thus they have a feebler depressant action on the central nervous system and they tend to relax smooth muscle; whereas morphine, in some animals at least, may stimulate smooth muscle. Opium, being a mixture of these alkaloids, acts in the main like morphine. Its preparations are given by mouth and therefore have a slower and more prolonged action than morphine, especially when the latter is given—as it frequently is—by hypodermic injection.

Preparations of Morphine and Opium. Like other alkaloids, morphine itself is insoluble in water, but its salts are soluble in varying degrees, so that morphine is usually prescribed in the form of one of its soluble salts; e.g. Morphinae Hydrochloridum, soluble in 1 in 24 of cold water, $\frac{1}{8}$–$\frac{1}{2}$ grain. A salt of morphine can be prescribed as required, but, for convenience, the B.P.

contains a *Liquor Morphinae Hydrochloridi*, 1 per cent., 10–60 minims, for internal administration; and an *Injectio Morphinae Hypodermica*, containing $2\frac{1}{2}$ per cent. of morphine tartrate (which is more soluble than the hydrochloride), given in doses of 5–10 minims by subcutaneous injection.

Opium may be given itself as a powder in doses of $\frac{1}{2}$–2 grains, or in the form of one of its numerous preparations. Of these only two may be mentioned. *Tinctura Opii* (Laudanum), containing 10 per cent. of opium or 1 per cent. of morphine, is given in doses of 5–15 minims if repeated, or 20–30 minims for a single administration. Where a weaker preparation is desired, e.g. in the treatment of cough or diarrhoea, *Tinctura Camphorae Composita*, B.P. (Tinctura Opii Camphorata, U.S.P.), which contains opium and aromatic substances, may be given in doses of 30–60 minims. It must be remembered that children, especially infants, are very intolerant of morphine or opium.

The opium alkaloids hitherto discussed are alkaloids which occur naturally in opium and can be extracted from it. Other alkaloids have been artificially prepared from morphine, of which two may be mentioned.

Diamorphine or **Heroine** is a diacetylmorphine, which very closely resembles morphine in action and has been widely used as a substitute for morphine. It is more powerful and has a smaller dose—Diamorphinae Hydrochloridum, B.P., $\frac{1}{25}$–$\frac{1}{8}$ grain.

It is very liable to give rise to a habit which is even more difficult to stop than the morphine habit.

Apomorphine is an artificial derivative of morphine formed from the latter by the action of certain dehydrating agents whereby it loses a molecule of water. This chemical change entails a considerable change in physiological action, for in apomorphine the

depressant action on the central nervous system is greatly enfeebled, while the stimulant action on some medullary centres, which is displayed to some extent by morphine in certain animals, is enormously enhanced. This is especially shown on the vomiting centre. In small doses apomorphine has little action beyond inducing vomiting and the usual concomitants of vomiting, e.g. increased bronchial and sweat secretion. Unlike most emetics (e.g. copper sulphate and ipecacuanha), it acts directly on the vomiting centre and thus can advantageously be given hypodermically. It acts very rapidly—within a few minutes—and is frequently used in cases of poisoning to empty the stomach. The hydrochloride of apomorphine is given in doses of $\frac{1}{20}$–$\frac{1}{10}$ grain hypodermically; often in the form of *Injectio Apomorphinae Hypodermica* (B.P.), 1 per cent., 5–10 minims.

Cannabis Indica.

The hemp plant, *Cannabis Indica*, has been used for centuries in Asia and Africa for its intoxicant or narcotic action. It is used in a variety of ways; frequently it is smoked like opium, which it resembles somewhat in action. It depresses the central nervous system and induces a condition of drowsy ease with a stimulation of the imagination. The power of estimating time and space is lessened or lost, and sensations of pain are diminished.

The chief importance of Indian hemp lies in its widespread abuse in the East as a narcotic. It gives rise to a habit, prolonged indulgence in which may give rise to mania or other nervous disorders. *Tinctura Cannabis Indicae* (5–15 min.) has been used medicinally to induce sleep, but is uncertain in action, partly from its poor keeping qualities.

X

DRUGS ACTING ON SENSORY NERVES

I. Stimulants of Sensory Nerve-endings

It is a very ancient and widespread practice to apply to the skin, as a remedial measure, substances which are found on investigation to have no property in common other than that of being irritants; but, though it is admitted that this practice often produces beneficial effects, there is still some doubt as to how precisely these effects are brought about. Irritation of the skin is in itself not a desirable condition, and it is now known that most of the beneficial effects produced by it are due to reflexes from the skin. As these arise from stimulation or irritation of the sensory nerve-ends in the skin, the group of skin irritants, *counter-irritants*, or *rubefacients* can conveniently be considered here.

When an irritant is applied to the skin, the skin becomes warmer and redder, and there may be some swelling. This is due to local dilatation of the arterioles and probably also of the capillaries, and is brought about by an axon reflex. The irritation of the skin causes an impulse to pass through the sensory nerve, which is reflected through the vasodilator nerve to the arterioles and causes them to dilate. This reflex is independent of the central nervous system and is prevented by local anaesthesia of the skin. The beneficial effects of irritants upon certain kinds of chronic inflammation of the skin and mucous membranes is mainly due to this vascular effect ('rubefacient action') accelerating repair by improving the local blood-supply.

In addition to this local vascular effect, irritation of the skin may produce an effect upon the general circu-

lation, for excitation (if not too severe) of any sensory nerve stimulates the vasomotor centre and produces a reflex rise of blood-pressure. The respiratory centre may also be stimulated. Many of the uses of skin irritants, such as the use of a mustard foot-bath in preventing the effects of chill, are no doubt due to an alteration of the blood-supply brought about by a general slight rise of blood-pressure added to a local dilatation of the blood-vessels.

Some of the uses of skin irritants cannot, however, be explained so simply, especially the influence of irritation of particular areas of skin upon the condition of particular internal organs. In this connexion the work of Head and Mackenzie has reconciled and explained some otherwise disconnected observations, examples of which will first be given in regard to one particular organ, the stomach. (1) Disease of the stomach is often associated with pain felt not in the stomach itself but over the epigastrium. (2) It had been found empirically that the application of a counter-irritant to the same area of the epigastrium (*a*) had often a favourable influence upon disease of the stomach and (*b*) relieved pain associated with gastric disease. (3) The only connexion between the stomach and the skin of the epigastrium is that the nerves of the stomach and the sensory nerves from the skin of the epigastrium both enter the same segment of the spinal cord.

It is supposed that an afferent stimulus may, if of sufficient intensity and duration, produce a condition of heightened sensibility in the segment of the cord which it enters. Thus, in regard to (1), abnormal impulses arising from a diseased stomach and producing a condition of heightened sensibility in the corresponding segment of the cord may affect neighbouring synapses in the segment, e.g. those belonging to the

sensory nerves to the skin which enter this particular segment. The irritation of the latter will be propagated to the brain and may give rise to sensations of pain, but which will be 'felt' in the skin of the epigastrium. This offers at any rate some explanation of 'referred' pain, (1) above, namely pain felt in a particular area of skin but due not to any pathological condition of the skin itself, but to a pathological condition of an internal organ.

If, under these conditions, an irritant be applied to the skin of the epigastrium, the afferent path for the stimuli arising from this point and leading to the perception area of the brain will be the same path as that of the referred pain associated with disease of the stomach. It is supposed that these new stimuli may occupy this path to the exclusion of the stimuli giving rise to referred pain, and this offers some explanation of (2 *b*), namely how the application of an irritant to the skin of the epigastrium may relieve pain associated with disease of the stomach.

There remains to be explained(2 *a*)—how can irritation of the skin of the epigastrium influence disease of the stomach? The same type of explanation can be given. Just as afferent impulses from the stomach may cause a spread of stimulus in a segment of the spinal cord so as to affect sensory nerves to the epigastrium, so conversely it is supposed that afferent stimuli from the epigastrium may spread in the cord so as to affect trophic and vasomotor nerves (efferent) to the stomach. It is conceivable, therefore, that the application of an irritant to the skin of the epigastrium may influence the trophic or vasomotor nerves going to the stomach and so modify pathological conditions in this organ. As to precisely what these influences are, we have little knowledge.

These considerations will perhaps supply some ex-

planation of the therapeutic uses of counter-irritants. They may be useful in chronic inflammations of the skin or subcutaneous tissues—from the improvement of the local blood-supply caused by the dilatation of the blood-vessels. Applied to the appropriate 'Head's Areas' of the skin, they may relieve pain due to disease of the corresponding internal organs or even favourably influence the progress of disease itself. From their method of action, it is not surprising that the beneficial effect of counter-irritants is apt to vary very much, and that their precise value is difficult to forecast, in different pathological conditions.

Many substances have been used as counter-irritants, those which have been singled out for preference being such as produce the desired amount of irritation of the skin within a reasonable time and without producing any permanent damage to the tissues. Of these may be mentioned some volatile oils (p. 175), especially oil of turpentine—*Oleum Terebinthinae Rectificatum*. This can be used in the form of *Linimentum Terebinthinae* (B.P.). *Linimentum Camphorae* (p. 178) acts similarly.

Mustard, which is frequently used medicinally and domestically as a rubefacient, owes its action to a volatile oil. Black mustard seeds, *Sinapis Nigra*, contain a glucoside and a ferment. In the presence of moisture the latter acts on the former and liberates the volatile oil of mustard, *Oleum Sinapis Volatile*. The pungency of mustard when used as a condiment and its irritant properties are due to this volatile oil. Ingested in large quantities mustard will produce vomiting, and is occasionally used as a reflex emetic. Applied to the skin, it will act as a counter-irritant. It may be so applied in the form of *Linimentum Sinapis* B.P. or *Emplastrum Sinapis* U.S.P.

Many other volatile substances, apart from the volatile oils, can be used as skin irritants; e.g. alcohol,

chloroform, ammonia, iodine. Some non-volatile substances have also been used, of which the most important is **Cantharidin**, an active principle found in Spanish fly (*Cantharis vesicatoria*) and in other species of Coleoptera. Cantharidin may produce any degree of irritation, from mere reddening of the skin to actual blistering, according to the concentration of it and the duration of application. It is chiefly used to raise a blister. Blistering has an effect on relief of pain similar to that of rubefacients. For this purpose a cantharides plaster (fly blister) *Emplastrum Cantharidini*, B.P., or *E. Cantharidis* (made from the powdered beetles), U.S.P., may be used. This plaster takes about 8–10 hours to raise a blister.

Cantharidin is rapidly absorbed from the alimentary canal or less readily from the skin. It may cause severe irritation of the alimentary tract if ingested, and of the genito-urinary tract when excreted in the urine.

II. Depressants of Sensory Nerve-Ends; Local Anaesthetics

Cocaine.

When the Spanish conquered Peru, they found that the Andean Indians were accustomed to chew the leaves of a shrub, *Erythroxylon Coca*. 'When I asked some of these Indians why they carried these leaves in their mouths, which they do not eat, but merely hold between their teeth, they replied that it prevents them from feeling hungry, and gives them great vigour and strength.' This early account of the coca leaf was found to be no mere traveller's tale, for scientific investigation has shown that cocaine, the chief alkaloid of the leaf, has actions which explain such statements, and which are indeed its main actions; for it stimulates the central nervous system and so relieves the sense

of fatigue, and, by its local anaesthetic action on the mucous membrane of the stomach, it relieves the sensation of hunger.

The stimulant properties of the coca leaf were recognized for over 300 years before the local anaesthetic action of its alkaloids was utilized. The alkaloid cocaine was isolated from the leaf in 1860 and its local anaesthetic action definitely demonstrated in 1880, when von Anrep found that, after injecting a solution of cocaine under the skin of the arm, the part became insensitive to the pricking of a needle, and that painting the tongue with a 1 per cent. solution caused loss of sensibility and of taste over the painted area. Four years later, Koller showed that instillation of a cocaine solution into the eye induced sufficient anaesthesia of the conjunctiva to enable painless operations on the eye to be performed. Since then the drug has come into general use as a local anaesthetic. Before this time no efficient local anaesthetics were known, and it is difficult to realize that the current methods of local anaesthesia, which now occupy such an important place in operative surgery, are entirely a product of the last forty-five years.

Though of less practical importance, the actions of cocaine on the central nervous system may be discussed before its local anaesthetic actions.

Cocaine is a powerful stimulant of the *central nervous system*, especially of the higher centres of the brain; but its action is not confined to these centres so exclusively as is the action of caffeine. Mental processes, so far as they have been measured, have been found to be temporarily facilitated by cocaine, and there is increased wakefulness and lessened sensation of fatigue, as with caffeine. But in other respects cocaine resembles atropine in its action, in stimulating motor areas as well. There is, for example, in man,

restlessness, increased movement, and talkativeness; and, experimentally in animals, the motor cortex is found to be more sensitive to stimuli. With increasing doses the action spreads downwards through the central nervous axis, causing a stimulation of the medullary centres, and eventually of the spinal cord. With poisonous doses convulsions are usually produced.

The stimulation of the nervous system is followed, if the dose be sufficiently large, by paralysis, affecting the centres nearly in the same sequence as the stimulation, the psychical centres being depressed first. Repeated doses of cocaine lead rapidly to the formation of a 'habit', and it is highly probable that the seductiveness of cocaine is due not entirely to the stimulant action (for no such habit is formed for caffeine) but is due partly to the depressant action on the higher centres. The latter may occur at a time when the rest of the nervous system is stimulated. In the case of acute poisoning by cocaine, the symptoms vary according to the dose and the speed of its absorption; the convulsions being sometimes so severe as to demand alleviation by chloroform, in other cases the symptoms being mainly those of paralysis. In any case, respiratory failure is usually the main cause of death, and artificial respiration is often successful in preventing a fatal issue. Especially if it should gain entrance into a vein, the cocaine is also highly toxic to the heart, and in this way death may occur within a few minutes.

Cocaine has also an action on *involuntary muscle*, generally first stimulating and then depressing it. The heart is quickened and the blood-vessels contracted by small doses. The constriction of the blood-vessels is seen in the blanching of the conjunctiva which results from the application of cocaine to it. The pupil, on the other hand, is dilated by cocaine, whether the latter reach the pupil from local application or from the

blood-stream. It has been thought that these effects are due to a stimulation of sympathetic nerve-ends, which would certainly explain the contraction of the vessels and dilatation of the pupil, but recent experiments have thrown doubts on this explanation.

Local Anaesthetic Action. This is the most important action of cocaine, and is due to the fact that cocaine has a specific paralysing action on sensory nerves. It temporarily abolishes conduction in them without seriously interfering with other cells with which it may come in contact. Applied to the surface of the tongue, a solution of cocaine paralyses first the receptors of pain, then those of touch, and lastly those of taste. When applied to a nerve-fibril or nerve-trunk, it will abolish conduction in them. If the nerve-trunk contain both afferent and efferent fibres, the former are paralysed earlier or by weaker solutions. As the cocaine is gradually absorbed into the blood, this action on the nerve passes off. Cocaine can thus be used to render a region of the body temporarily anaesthetic, so as to admit of operations being performed on that part. The difference between such local anaesthesia and general anaesthesia is that, in the former case, pain is abolished only of a limited region of the body and by an action on the peripheral nerves, and there is no unconsciousness. A general anaesthetic acts on the central nervous system, abolishes pain over the whole body, and, in full anaesthesia, abolishes also consciousness and reflex activity.

According to the part of the afferent path to which it is applied, cocaine can be used to produce anaesthesia of varying extents of the body. For convenience, we may consider four possible types of local anaesthesia, recognizing that those do not involve any difference in the action of cocaine but only an alteration in the site of its application.

1. *Surface Anaesthesia.* When a solution of cocaine hydrochloride is applied to a mucous membrane, afferent conduction from the affected area is abolished. For example, if applied to the nasal mucous membrane, cocaine not only renders the mucous membrane insensitive to pain and touch, but also abolishes the sense of smell. A solution of cocaine does not easily penetrate the epidermis, so that it produces very little effect on unbroken skin, but if an ointment of cocaine be rubbed into the skin, some local anaesthesia is produced. These superficial actions of cocaine are due to its paralysing the afferent nerve-ends or possibly the commencing fibres of the nerve itself.

2. *Hypodermic Anaesthesia.* When cocaine is injected under the skin or mucous membrane, it comes in contact with the smaller nerve-fibrils. These are readily paralysed by cocaine. A local area of anaesthesia develops, the extent of which depends upon the number of afferent fibrils which the cocaine reaches and upon the area from which they conduct sensation.

3. *Regional Anaesthesia.* The smaller nerve-fibrils coming from different areas of skin join together to form larger and larger nerve-trunks. If cocaine be applied to a large afferent nerve-trunk it will therefore render anaesthetic a large area, the extent of which depends upon the fibrils which have their conduction abolished. Applied, for example, to the sciatic nerve, cocaine will destroy the sensibility of more or less of the corresponding lower limb.

4. *Spinal Anaesthesia.* If a cocaine solution be injected into the subdural space of the spinal cord, e.g. by passing a long injecting needle between the laminae of the lumbar vertebra, the posterior nerve-roots with which it comes in contact are paralysed, and this abolishes sensation in their peripheral distribution. Anaesthesia of the lower limbs and of an extent of

trunk depending upon the site of injection can thus be induced.

By these different methods, all of which are in use, sensation of varying regions of the body can be abolished, and painless operations done on these areas.

Usually when a hypodermic injection is given, it is given with the definite intention that the injected substance should be absorbed, and this absorption cannot be prevented when cocaine is injected. In the early days of its use, cocaine sometimes caused serious and even fatal accidents from the poisonous effects it produced after absorption. This danger has now largely disappeared as the result of the practice of adding to the cocaine solution a small quantity of adrenaline. The effect of adrenaline is to constrict the arterioles of the injected area, whereby it produces three salutary effects, all due to vasconstriction, which diminishes, or for a time may even stop, the local circulation. In the first place, haemorrhage is lessened. In the second place, absorption of cocaine into the general circulation (the rate of which depends upon the efficiency of the local circulation) is slowed, so that (*a*) less cocaine is needed to produce anaesthesia and (*b*) the anaesthesia lasts longer. In the third place, as the rate of absorption of cocaine is diminished, while the rate of its excretion is unaltered, the concentration in the blood does not reach so high a level as it would do if cocaine were injected without adrenaline, so that the risk of general poisoning by cocaine is lessened.

Though the addition of adrenaline has materially reduced the dangers of cocaine injections, it has not entirely removed them. There remains still the danger, for example, of the combined solution accidentally entering a vein; and both adrenaline and cocaine are very much more toxic by intravenous than by hypodermic injection. Attempts have, therefore, been

made to discover substances which would possess the local anaesthetic action of cocaine with a diminished general toxicity. Though much progress has been made in this direction, a local anaesthetic ideal for all purposes has not yet been discovered, for usually one which avoids the drawbacks of cocaine introduces drawbacks of its own. Three of these *newer anaesthetics* may be mentioned: novocaine, eucaine, and stovaine. All of these possess one advantage over cocaine in that solutions of them can be sterilized by boiling, whereas cocaine is a relatively unstable substance which is decomposed and inactivated by boiling. Cocaine is still the best for producing surface anaesthesia, partly because it penetrates the mucous surface so much better. **Novocaine**, while less valuable for this purpose, is very efficient when injected, and is less toxic than cocaine, so that it is largely used for injection methods of anaesthesia. **Stovaine** is chiefly used for spinal anaesthesia, for which purpose it seems to be less toxic and more suitable than cocaine.

Cocaine is generally used as the hydrochloride, *Cocainae Hydrochloridum*, which forms colourless crystals soluble in water. It is very rarely given internally ($\frac{1}{10}$–$\frac{1}{4}$ gr.). As a local anaesthetic, it is used in varying strengths of solution, according to the depth and duration of anaesthesia required and the region to which it is applied. For example, to allay pain in the conjunctiva a 1 per cent. solution may suffice, whereas for complete anaesthesia of the eye 4 per cent. may be necessary. Stronger solutions may be applied to limited areas of the nose or larynx. Poisoning may occur from absorption from a mucous surface, especially from the urethra.

The danger of habit formation with cocaine must always be kept in mind. It is a habit which rapidly leads to mental and moral deterioration and is un-

fortunately widespread though it can hardly be called prevalent. *Habitués* usually take it as a snuff, for it is rapidly absorbed from the nasal mucous membrane, and so produces its action on the central nervous system. The chief symptoms arising from repeated indulgence in cocaine are loss of appetite, emaciation, sleeplessness, tremors, hallucinations, and finally more serious mental symptoms. The substitutes for cocaine do not seem to induce habit formation.

Other Local Anaesthetics

Before the introduction of cocaine, several other substances were used as surface local anaesthetics. For example, opium, belladonna, aconite, hydrocyanic acid, and menthol were all applied locally to the skin for the relief of pain. Though not very effective, they are still occasionally used for this purpose. Of those mentioned, aconite and hydrocyanic acid have nowadays hardly any place in therapeutics beyond their occasional use as surface anaesthetics, and they may therefore be considered here.

Aconite.

The poisonous nature of Aconites was known to the Greeks, and some species of Aconite were used by Asiatic tribes as arrow poisons. Aconite (all parts of the plant are physiologically active) was introduced into European medicine about the middle of the eighteenth century, as a remedy for gout and rheumatism. Later it came to be used as an anodyne, and later still as febrifuge. For the latter uses it has been largely replaced by the newer local anaesthetics and antipyretics, so that it is now an unimportant drug.

The actions of aconite are mainly due to the very poisonous alkaloid *aconitine*. The most remarkable effects of aconite are due to its specific action on

afferent nerve-ends, which it first stimulates and then depresses. When swallowed, aconitine produces tingling of the lips, tongue, and stomach, and, if it be absorbed, even of the skin. Later this tingling, which is due to stimulation of sensory nerve-ends, is replaced by numbness, due to their paralysis. This action is the basis for the use of aconitine as a local anaesthetic.

Aconitine also causes a fall of temperature both in normal and febrile animals. Exactly how it does this is unknown, but it affords a pharmacological justification for the use of aconite as an antipyretic. Aconitine has a complicated, and so far not very carefully analysed, action on the central nervous system. Its main action is first to stimulate and then depress the medullary centres. It has been used to slow the pulse especially in febrile conditions, which it does by stimulating the vagus centre. Respiratory failure is the chief cause of death from aconite.

Preparations of aconite or aconitine are occasionally used externally for the relief of neuralgia. *Tincture of Aconite* (5–15 m. or 2–5 m. if frequently repeated) is sometimes given internally to slow the pulse or lower the temperature.

Hydrocyanic Acid is now almost exclusively, and that rarely, used as a surface anaesthetic. This, as well as its other actions, is due to the -CN ion, as compared to which its mere acidity is of slight importance; and the actions to be described are possessed also by any simple ionizable cyanide like potassium cyanide, but not by double cyanides like potassium ferrocyanide, in which the -CN ion is not ionizable as such.

Applied to the skin or to a mucous surface, a dilute solution of prussic acid produces a dulling of sensation due to its paralysing sensory nerve-ends. Owing to its rapid evaporation, it cannot conveniently be applied to the skin, besides being an inefficient

anaesthetic for skin surfaces. It is chiefly used as a sedative in two conditions: in gastric pain, with or without vomiting, and in cough. Its disputed value in the former is explainable by its local anaesthetic action on the mucous membrane of the stomach. The amount usually given for the relief of cough (and usually given with other more energetic substances so that the precise contributory effect of the hydrocyanic is difficult to estimate) is probably too small to produce any direct effect on the respiratory centre or bronchi. Its reputation for relieving cough may be due to its local anaesthetic action on the pharynx and stomach, whereby it may check that variety of cough which is due to reflex pharyngeal or gastric irritation.

In any case, it has but a precarious reputation as a local anodyne and no established therapeutic value for any action that it can exert after absorption. A slight notice of its general actions is, however, due to its well-merited reputation as a potent and very rapid poison. The fatal dose in man is about one grain of the pure acid. Quantities much above this produce almost instantaneous death. Even with less rapidly acting doses the symptoms are difficult to analyse, because hydrocyanic acid is so general a poison that all tissues are more or less involved. Probably its chief action, however, is on the subcortical regions of the central nervous system, which it first stimulates and then paralyses. The stimulant action of small doses on the respiratory centre is well marked, and it has even been suggested that they might be used therapeutically for this purpose. Large doses very rapidly paralyse the respiratory centre. Attention has often been drawn to the fact that, in cases of fatal poisoning by prussic acid, the blood retains a bright red colour. This may be partly due to the formation of a compound with haemoglobin (cyano-haemoglobin) that is reduced

with difficulty, but chiefly to the fact that hydrocyanic acid exerts a remarkable effect on the tissue-cells, whereby they are unable to take up oxygen from oxyhaemoglobin, which therefore remains unreduced and of its normal bright red colour. For medicinal use the preparation employed is *Acidum Hydrocyanicum Dilutum*, a 2 per cent. solution when fresh.

Many plants contain glucosides, which under the action of an appropriate ferment, or when otherwise split up, liberate among other things hydrocyanic acid. Of these the **virginian prune**, the **bitter almond**, and especially the **cherrylaurel** leaf have been used to make medicinal preparations. Such preparations are superfluous, as any action they exert is due to the prussic acid.

Drugs acting on Motor Nerve-Ends in Voluntary Muscle

We have had examples both of drugs which stimulate and of drugs which paralyse sensory nerve-endings. Substances are also known which stimulate or depress the motor nerve-ends in voluntary muscle, but as those actions cannot well be employed for any therapeutic purpose, a passing mention of these substances is all that is needed here.

Physostigmine (which has other more important actions, *v.* p. 132) in large doses causes fibrillary twitchings in voluntary muscle, due to stimulation of the motor nerve-endings, but could not well be used for this purpose even if any pathological condition were known in which such an action might be beneficial.

Many substances are known which paralyse motor nerve-endings in voluntary muscles. This is the chief physiological action, for example, of the arrow poison **curara**. In sufficient doses it will cause complete

paralysis of all voluntary muscles. Hence its use has been suggested for the suppression of convulsions, but it cannot safely be used for this purpose because the respiratory muscles are paralysed like other striped muscles.

XI

DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM

A. Parasympathetic Nerves

The vegetative processes of the body, which are carried on usually without raising conscious sensations, have their activities controlled by a special system of nerve-cells and nerve-fibres—the autonomic nervous system. As the cumulative result of many experiments and observations, it has been found that the whole autonomic nervous system is divisible into two units, to which the terms sympathetic and parasympathetic are now applied. The recognition of these two natural divisions has been of immense importance for physiology and medicine generally, and has also simplified our conceptions of the actions of many important drugs. It may facilitate an understanding of the action of these drugs if one recalls a few of the pertinent facts in regard to the autonomic nervous system and the organs it supplies.

While the voluntary muscles are supplied by the central nervous system proper, the involuntary muscles are under control of the autonomic nervous system. The latter system therefore supplies involuntary muscle wherever it is found—in the heart, blood-vessels, bronchi, alimentary canal, uterus, and so on. Practically all that is left of the active vegetative organs of the body consists of glands of some form or other. When a drug acts on the autonomic nervous system, this action will therefore be exhibited mainly on two kinds of organs—(*a*) involuntary muscle, and (*b*) glands.

Nearly every involuntary muscle and every gland is found to have a double nerve-supply, one from the sympathetic, and the other from the parasympathetic, division. In the case of some organs this double supply was early discovered, e.g. the sympathetic and vagus nerves to the heart; in the case of less important organs this double nerve-supply has been sought for (and usually found) only within very recent years. It may be helpful to remember that this division of the whole autonomic system into two branches is based upon anatomical, physiological, and pharmacological differences between the two, some of which will be mentioned.

Differences between Sympathetic and Parasympathetic Nerves.

1. **Anatomical.** The sympathetic nerves arise from the dorso-lumbar part of the spinal cord; the parasympathetic from the mid-brain, medulla oblongata, and sacral part of the spinal cord. The peripheral ganglia of the parasympathetic nerves are usually close to the organs they supply, those of the sympathetic nerves remote from the organ, i.e. nearer to the central nervous system. The parasympathetic nerves tend to aggregate into larger nerve-trunks which, being more noticeable, have received special names. Indeed, nearly all the involuntary muscles and glands receive their parasympathetic nerve-supply from one of four nerve-trunks, the oculomotor, chorda tympani, vagus, and pelvic nerves. The sympathetic nerves on the other hand usually run in more numerous but smaller trunks, which frequently have no special name other than the sympathetic branch to the organ.

2. **Physiological.** Stimulation of the sympathetic nerve to an organ has usually an effect different from that of stimulation of its parasympathetic nerve, e.g.

stimulation of the cardiac sympathetic nerve causes acceleration and augmentation of the heart, whereas stimulation of the vagus causes slowing and depression. In the case of the heart, therefore, the nerves are physiological antagonists, and so they are usually. One of the chief difficulties in regard to the autonomic nervous system is, however, that though the sympathetic and the parasympathetic nerves to a particular organ usually have antagonistic actions, it is not always the sympathetic nerve which is the motor one and the parasympathetic the inhibitor (as in the heart), for, in the case of the bronchi for example, the vagus is the motor and the sympathetic nerve the inhibitor nerve. Hence a drug like adrenaline, which stimulates sympathetic nerves, has a motor effect on some organs and an inhibitor effect on others, depending on what happens to be the effect of sympathetic stimulation on the particular organ.

3. **Pharmacological.** The evidence of pharmacology goes far to confirm the essential separateness of the sympathetic and parasympathetic nerves, because it is found that a drug which acts on sympathetic nerves need not, and usually does not, have any action on parasympathetic nerves, and vice versa. Further, a drug which acts on the sympathetic nerve to one organ usually acts in a similar fashion on sympathetic nerves in all organs, and the same is true of the action of drugs on parasympathetic nerves. This goes far to show that the nerves now grouped as sympathetic nerves form a homogeneous whole, and similarly with those grouped as parasympathetic nerves. From the point of view of the therapeutic uses of drugs, this is often a disadvantage, for it usually prevents one being able to influence one organ exclusively; for example, when pilocarpine is given to increase sweat secretion, it cannot be prevented from stimulating bronchial

secretion at the same time, though this latter action may be in a particular instance undesirable.

Though drugs are known, nicotine for example, which act on the autonomic nerve ganglia, none of these are of sufficient therapeutic importance to require mention here. Those that are now to be dealt with all act on the peripheral terminations of the autonomic nerves, that is, where the nerves enter the gland or muscle. Much discussion has centred round the precise point of action of these drugs, as to whether it is the actual nerve-ending that is acted on or something between this and the muscle or gland. What is important is that a drug which is described as stimulating the termination of an autonomic nerve produces the same effect as would be produced by stimulating the trunk of that nerve, e.g. by an electric current, an effect which may or may not be the same as stimulation of the muscle or gland directly.

As the sympathetic and parasympathetic nerves have often opposite actions, it will clearly make all possible difference in the case of a drug whether it acts on the one or the other. Also, the endings of either may be stimulated or paralysed, and important examples of all possible actions are known. The following table makes this preliminary classification of the drugs we have to consider.

Parasympathetic nerve-ends.		*Sympathetic nerve-ends.*	
Stimulate.	*Paralyse.*	*Stimulate.*	*Paralyse.*
Pilocarpine	Atropine	Adrenaline	
Physostigmine	Hyoscine	Tyramine	
		Ergotoxine (in small doses)	Ergotoxine (in large doses)

As the student is probably more familiar with the parasympathetic than with the sympathetic nerves,

we may begin with the former, and in accordance with the plan generally followed in this book we shall take first

I. Drugs which stimulate Parasympathetic Nerve-Ends

Pilocarpine is an alkaloid obtained from Pilocarpus jaborandi, a shrub growing in Brazil, the leaves of which were introduced into modern medicine, in 1875, for their diaphoretic action. Pilocarpine stimulates all parasympathetic nerve-endings and produces effects similar to simultaneous stimulation of all the parasympathetic nerves. We need mention only the more important of these effects.

In regard to *involuntary muscle*, pilocarpine, by stimulating the terminations of the third nerve, causes contraction of the sphincter pupillae and therefore makes the pupil smaller; it also causes contraction of the ciliary muscle, thereby fixing accommodation at the focus for short distance; intra-ocular tension is lowered after a preliminary rise. These effects on the eye are produced not only when pilocarpine circulates in the blood but also when it is applied in solution to the conjunctiva. By stimulating vagal nerve-ends, pilocarpine slows the heart, constricts the bronchi, and augments the movements of the stomach and intestine. It also stimulates uterine movements although, so far, no parasympathetic nerves to the uterus have been discovered.

In regard to *glands*, pilocarpine stimulates the secretion of the salivary, buccal, bronchial, lachrymal, and enteric glands. It has no effect on the mammary gland because the mammary gland has no nerve-supply, and pilocarpine does not stimulate glands unless via the nerve. It also stimulates the sweat glands, though these appear to have only sympathetic

nerves. This is a curious discrepancy which shows that the correspondence between the action of pilocarpine and the effect of parasympathetic nerve stimulation is not absolute.

Once pilocarpine enters the circulation, it acts on all these terminations, but in the smallest effective doses it acts more on glands than on smooth muscle. With the latter doses, therefore, the chief noticeable symptoms are increased salivation, sweating, and bronchial secretion. Larger doses may slow the heart and augment the movements of the stomach and intestine, and may produce vomiting and diarrhoea. Poisonous doses embarrass the respiration (from constriction of the bronchi and blocking of their lumen by secretion) as well as the circulation (from cardiac slowing). In many animals convulsions precede death.

(**Muscarine,** an alkaloid obtained from poisonous mushrooms, and **Arecoline,** an alkaloid obtained from Betel Nut, have actions similar to pilocarpine, but are not used in regular medicine.)

Physostigmine is an alkaloid obtained from the seeds of *Physostigma venenosum* (Calabar Bean), a tall climbing plant growing round the Gulf of Guinea. The Calabar bean was used by the tribes of Tropical West Africa as an 'ordeal' poison. It was introduced into modern medicine in 1863 for constricting the pupil, and later it was found that this action on the pupil, due to stimulating the terminations of the third nerve, was only one instance of the general action of physostigmine, which stimulates all other parasympathetic nerve-ends as well. Its peripheral actions are therefore qualitatively like those of pilocarpine. There is a quantitative difference, however, in that physostigmine acts rather more powerfully on involuntary muscle than on glands, whereas the reverse, as we have seen, is true of pilocarpine. Indeed,

physostigmine seems to have some direct stimulating action on smooth muscle in addition to its indirect nervous action.

Toxic doses of physostigmine produce, as one would expect from its action, complicated effects arising from cardiac slowing, broncho-constriction, and violent contractions of the alimentary canal. In addition it paralyses the central nervous system, causing death mainly by respiratory failure.

Therapeutic uses of Pilocarpine and Physostigmine.

From what has already been said, it will be intelligible that pilocarpine is used mainly for stimulating gland secretions. It must be used with care, but with smallest doses the action on glands can be obtained without any serious cardiac slowing or bronchial constriction. It is used chiefly for increasing sweat secretion in serious diseases of the kidney, for it is one of the most powerful of known diaphoretics; less frequently it is used as an expectorant, for which effect there are numerous and safer substitutes. Though, in prescribing it, one may desire only its diaphoretic action, it is not possible to escape its action on the bronchial and other glands, and this is often a disadvantage as compared with other methods of producing diaphoresis.

Physostigmine is chiefly used for its action on the eye. Applied to the conjunctiva, it diffuses through and stimulates the ends of the third nerve in (*a*) the sphincter pupillae and (*b*) the ciliary muscle. It therefore (*a*) contracts the pupil, and (*b*) produces spasm of accommodation, the contraction of the ciliary muscle fixing accommodation at the focus for short distance. But physostigmine is not used therapeutically for these effects so much as for its indirect effect in lowering intra-ocular pressure in diseases such as glaucoma,

where the intra-ocular tension is dangerously high. This fall of pressure may last about 12 hours, and is generally ascribed to the opening up of the spaces of Fontana (by the contraction of the pupil) allowing freer escape of fluid.

Another important use of Physostigmine is to stimulate the movements of the intestine. It is thus used (by hypodermic injection and especially in combination with pituitrin) to rouse the dormant contractions of the gut in post-operative intestinal atony.

The official salt of pilocarpine is *Pilocarpinae Nitras* (sol. 1 in 9 cold water) $\frac{1}{20}$–$\frac{1}{5}$ grain; and of physostigmine, *Physostigminae Sulphas* B.P. or *Salicylas* U.S.P., $\frac{1}{50}$–$\frac{1}{20}$ gr. For application to the eye, physostigmine is commonly used in a solution of 0·1 to 1·0 per cent.

II. Drugs which Paralyse Parasympathetic Nerve-Ends

Atropine.

Atropine is the chief alkaloid found in the leaves and root of *Atropa belladonna*, a plant of the order of Solanaceae. Many other species belonging to this natural order contain either atropine or some nearly related alkaloid.

Atropa belladonna, a tall striking perennial herb, a native of Central and South Europe and a doubtful native of England, received its name *Herba belladonna* so early as the sixth century from its use, by the 'fine ladies' of Venice, for the purpose of imparting lustre to the eyes by dilating the pupil. This use illustrates one of its main actions. Though the plant was recognized as a poison, it did not come to be used in medicine till late in the eighteenth century, when it began to be employed in whooping cough and for its mydriatic action. Later it came to be used as a local anodyne.

The actions of belladonna are due mainly to the atropine in it.

Atropine is composed of a tropine and tropic acid radicle, tropine very nearly resembling the ecgonine radicle in cocaine. Atropine is a mixture of dextro and laevo hyoscyamine. As is so often the case with alkaloids, the laevo compound is much more active than the dextro, so that the action of atropine is mainly that of the laevo half. As laevo hyoscyamine is difficult to obtain pure and has not come into general use and has qualitatively much the same actions as atropine, we need consider here only the actions of the natural mixture of laevo and dextro hyoscyamine, viz. atropine.

Atropine paralyses parasympathetic *nerve-ends*, and therefore has actions opposite to those of pilocarpine. To facilitate comparison, we may consider its actions in the same order as was adopted in the case of pilocarpine, taking first effects on smooth muscle and then effects on glands.

By paralysing the terminations of the third nerve in the sphincter pupillae, atropine dilates the pupil; the ciliary muscle, also supplied by this nerve, is likewise paralysed, leading to paralysis of accommodation, it being impossible to focus for near objects; intraocular tension is raised. These ocular effects occur either when atropine is applied locally to the conjunctiva or when it circulates in the blood. By paralysing the terminations of the vagus, atropine produces the following effects. The heart is quickened, the bronchi are relaxed, and exaggerated movements of the alimentary canal are diminished. In regard to the heart, the vagal paralysis produced by atropine prevents inhibitory impulses from the vagus centre reaching the heart. The amount of acceleration produced will therefore depend upon the degree of inhibi-

tion present, which will vary according to the species and age of the animal.

By paralysing the terminations of the nerves of most secreting glands, e.g. salivary, bronchial, lachrymal, and sweat glands, atropine diminishes their secretion.

In addition to these peripheral actions, atropine also acts on the *central nervous system*, stimulating first the medullary centres and later the motor areas of the cortex. Toxic doses paralyse the central nervous system eventually, the respiratory centre failing first.

The symptoms of *poisoning* by belladonna or atropine are the result of (*a*) the peripheral and (*b*) the central actions described above. There is (*a*) dryness of the mouth and throat, with thirst and difficulty of swallowing and speaking; dryness of the skin sometimes with an erythematous rash; dilated pupils with indistinctness of vision due to paralysis of accommodation: and (*b*) restlessness and garrulousness and eventually even convulsive movements, due to stimulation of the motor areas of the brain. Later the central nervous system may be depressed, and the patient may become paralysed and, if the dose be fatal, die mainly from paralysis of the respiratory centre.

Therapeutic uses of Atropine. Atropine is used in ophthalmological work, e.g. to dilate the pupil for diagnostic purposes or to paralyse accommodation in inflammatory conditions of the iris. Larger quantities are needed to paralyse the ciliary muscle than suffice to paralyse the sphincter pupillae. One drawback to atropine for many purposes is its prolonged action, for the pupil may not recover its normal size or reactivity for several days. The fact that atropine raises intraocular pressure must always be kept in mind, for this often precludes its use.

For its action in paralysing the vagal ends in the bronchi, atropine is sometimes used in spasmodic asthma (which is usually due to reflex spasm of the bronchi). The early use of it in whooping cough, for which it is sometimes still employed, may find an explanation in the same action. Atropine can also be used to relieve colic or to prevent spasmodic contractions of the gut. It acts similarly on the urinary bladder, and is often useful in incontinence of urine when this is due to hyperexcitability of the bladder reflex.

For its action on glands, atropine is occasionally used to diminish bronchial or sweat secretion. A drawback to its use for this purpose is that it acts on so many organs at once, and its action cannot be confined to one set of glands exclusively.

The official salt of Atropine is the sulphate, *Atropinae Sulphas* $\frac{1}{200}$–$\frac{1}{100}$ grain. The B.P. contains a solution—*Liquor Atropinae Sulphatis*, 1 per cent., $\frac{1}{2}$–1 min., and *Lamellae Atropinae*, gelatin disks containing $\frac{1}{5000}$ grain of atropine sulphate, used for application to the eye. For internal administration *Tincture Belladonnae* (5–15 min.) may be used in mixtures or *Extractum Belladonnae* ($\frac{1}{4}$–1 gr.) in pills.

Homatropine, an artificial compound of tropine and oxytoluic acid, is sometimes used as a substitute for atropine in ophthalmic practice. When applied to the eye it dilates the pupil almost as quickly as atropine, but its action passes off much sooner, e.g. in about 24 hours. It is more convenient than atropine for examination of the eye, and has less tendency to increase intra-ocular pressure. It may be used in the form of a solution of the hydrobromide or of a lamella ($\frac{1}{100}$ gr. in each B.P.).

Many other plants, belonging like belladonna to the natural order Solanaceae, have been found to resemble

it in containing atropine or alkaloids closely related to it. Of these plants the most important is *Hyoscyamus*, the leaves of which contain two alkaloids, **Hyoscyamine,** resembling atropine in action, and Hyoscine (also called scopolamine). **Hyoscine** resembles atropine in its peripheral actions, i.e. it paralyses the terminations of parasympathetic nerves, and produces the effects on smooth muscle and on secretions which have been described under atropine. It differs from atropine, however, in its action on the central nervous system, which it depresses from the outset without the previous stimulation that is seen with atropine. It produces sleep with a marked diminution of motor excitability. It is used chiefly in controlling the excitement of insanity and delirium tremens or for relieving the tremor of paralysis agitans. For such purposes hyoscine hydrobromide is usually given subcutaneously in doses of $\frac{1}{200}$–$\frac{1}{100}$ grain. Hyoscine is also used in combination with morphine to produce narcosis and analgesia ('twilight sleep') especially in childbirth.

An extract and a tincture of Hyoscyamus leaves are also used, *Extractum* and *Tinctura Hyoscyami*, most frequently to relieve colic. *Tincture of Stramonium*, made from the dried leaves of *Datura Stramonii*, a plant belonging to the same natural order as Hyoscyamus, is sometimes used for much the same purposes as tincture of hyoscyamus.

XII

DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM (*cont.*)

B. Sympathetic Nerves

Adrenaline *or* **Epinephrine.**

The discovery by Oliver and Schafer in 1901, that intravenous injection of an extract of suprarenal gland caused a remarkable rise of blood-pressure, has been one of the most fertile starting-points for physiological research of the twentieth century. Subsequent researches have shown that this effect is due to the presence in suprarenal gland-extract of an active principle—adrenaline; that the pressor effect is due to the fact that adrenaline stimulates vasoconstrictor nerve-terminals; and that it stimulates not these only but also sympathetic nerve-terminals in almost every organ of the body. When adrenaline is injected into a vein, therefore, it produces a great variety of effects such as would be produced by simultaneous stimulation of all the true sympathetic nerves. This generalization in regard to the similarity between effects produced by adrenaline and by sympathetic stimulation has only been rendered possible by a great number of investigations; but now that the generalization can be made, the various actions of adrenaline can at once be summarized, provided only that one knows what organs receive a sympathetic nerve-supply and what are the effects of sympathetic stimulation upon them.

The action of adrenaline on the heart and blood-vessels may be dealt with first, as being first both in historical and in therapeutic importance. The rise of

blood-pressure produced by adrenaline is steep and high, but lasts only for a few minutes. It is mainly due to contraction of the arterioles, as can be shown by the fact that the rise of pressure is accompanied by a diminution of intestinal volume. Adrenaline contracts blood-vessels when applied locally to them or when perfused through an organ removed from the nervous system, i.e. it is a peripheral action. The vaso-constrictor supply to the heart, lungs, and brain is feeble or absent, and, correspondingly, adrenaline produces little or no constriction of the vessels to these organs.

The isolated perfused mammalian or batrachian heart is augmented and accelerated by adrenaline, just as by stimulation of the cardiac sympathetic nerve. In the intact animal, however, especially at the height of the rise of blood-pressure, the heart may be slowed. This is due to reflex slowing of the heart produced by the rise of pressure, which may overcome the direct accelerating effect of adrenaline on the heart itself.

On involuntary muscle elsewhere adrenaline also produces effects like sympathetic stimulation. Injected intravenously it dilates the pupil, by stimulating the sympathetic terminals of the dilator pupillae. It dilates the bronchi if they are not already completely dilated. The splanchnic nerve (the sympathetic nerve to the alimentary canal) sends inhibitory fibres to the stomach and intestine, with exception of the pyloric and ileocolic sphincters and the muscularis mucosae, to which the fibres are motor; similarly adrenaline inhibits the tone and movements of the alimentary canal generally, but increases the contractions of these sphincters and of the muscularis mucosae.

The action of adrenaline on the uterus differs in different species of animals. Thus the human uterus and the uterus of the rabbit contract, while the

uterus of the guinea-pig and rat relaxes, in both instances whether the uteri are pregnant or not. The uterus of the cat contracts only when pregnant and relaxes when not pregnant.

In each case the same effect is produced by stimulation of the sympathetic (hypogastric) nerve in these animals.

The complete correspondence between the actions of adrenaline on different areas of the alimentary canal and on the uteri of different animals and the effects of sympathetic stimulation on these organs furnishes two of the many cogent arguments for the belief that adrenaline stimulates sympathetic nerves rathers than acts on muscle directly, for in the latter case it would cause probably either always contraction or always relaxation of the muscle.

On glands the action of adrenaline is not so important as is that of pilocarpine, for, generally, glandular secretions are influenced less by sympathetic than by parasympathetic stimulation, so that, at least so far as its therapeutic actions are concerned, only the actions of adrenaline on involuntary muscle are important.

Therapeutic uses of Adrenaline. Adrenaline is widely used as a local haemostatic. For example, it can be applied to the nasal mucous membrane to stop bleeding from the nose, or it can be given by the mouth to arrest bleeding from the stomach. It stops bleeding by causing extreme constriction of both arteries and veins. Its use with cocaine has already been referred to.

It is used to raise blood-pressure and stimulate the heart in some kinds of circulatory failure (but not in that occurring in the early stages of chloroform anaesthesia, when it may add to the risk of ventricular fibrillation). Though in the normal animal adrenaline produces only a very transient rise of pressure, in some

abnormal conditions of low pressure it may produce a lasting rise.

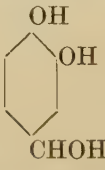
It is used in that variety of asthma which is due to spasmodic contraction of the bronchioles. Here doses of 2 to 10 minims of the liquor are given subcutaneously. For contracting the uterus it is inferior to pituitary. It is to be remembered that adrenaline has little or no effect on the blood-pressure when given by mouth. This is due chiefly to its rapid destruction in the alimentary canal.

Adrenaline is usually administered in the form of *Liquor Adrenalini Hydrochloricus* (B.P.); *Liquor Epinephrinae Hydrochloridi* (U.S.P.), a 1 in 1,000 solution of the hydrochloride. For hypodermic or intramuscular injection the usual dose is 2–10 minims. For intravenous injection the dose is much smaller, 1–2 minims, which must be well diluted with saline solution and injected very slowly.

Other Sympathomimetic Amines.

As has already been pointed out, adrenaline produces effects which resemble those produced by stimulation of the sympathetic nerves. Many other substances have been found to have the same action, and for this type of action the term 'sympathomimetic' has been used. Especially many amines, and in particular those having a constitution closely resembling adrenaline itself, possess this type of action.

The constitutional formula for adrenaline is



and it has been synthesized artificially. One relative

of adrenaline, **Tyramine**, requires special mention, because of its occurrence in ergot and elsewhere. Tyramine is parahydroxyphenyl ethylamine with the formula

It can be formed from the amino-acid tyrosine by splitting off CO_2. This is the usual method by which an amine is formed from the corresponding amino-acid.

Tyramine acts like adrenaline in stimulating sympathetic nerve-ends. It differs from it in acting more strongly on motor than on inhibitor sympathetics. It is also less readily destroyed, so that some effect on blood-pressure can be obtained by it when given subcutaneously or even by mouth.

Ephedrine, an alkaloid obtained from Ma Huang, a drug which has long been in use in China, is closely related to adrenaline

$$= C_6H_5 . CHOH . CHCH_3 . NHCH_3 .$$

Ephedrine is more stable than adrenaline and is active when given by mouth. It resembles adrenaline in action but seems to have a direct stimulant action on arterial muscle. It is being tried as a substitute for adrenaline especially in cases where it would be advantageous to give the drug orally.

Ergotoxine and **Ergotamine** are two alkaloids found in ergot (*v. infra*). They act similarly, and their actions are difficult to explain. They provoke contractions of involuntary muscle of many organs but not of all. This renders it improbable that they act directly on smooth muscle. They are now believed to

stimulate sympathetic nerve-ends, but only when these are motor. They thus differ from adrenaline, which stimulates inhibitor as well as motor sympathetics. The most important actions of ergotoxine and ergotamine are therefore to stimulate the uterus and to raise blood-pressure.

In large doses they paralyse motor sympathetic nerve-ends, but this does not occur with therapeutic doses.

Ergot is a parasitic fungus (*Claviceps purpurea*) which grows on the ovary of the rye or on other kinds of grain. As the result of this growth, the rye grains become swollen and purplish in colour. Bread made from rye thus infected has occasionally given rise to epidemics of chronic poisoning, especially in eastern Europe. In some of these epidemics gangrene of the fingers or toes, or more rarely of other organs, has been a prominent feature. Abortion sometimes occurs in pregnant women. This latter effect has possibly suggested the medicinal use of ergot, which began to be regularly used in obstetrics about the middle of the nineteenth century.

The chief active principles of ergot are the alkaloids ergotoxine and ergotamine mentioned above. It also contains small and variable amounts of certain amines, especially tyramine (*v.* p. 143) and histamine (*v.* p. 149). All these substances, though they differ in other actions, agree in stimulating the pregnant uterus, and it is for this action on the uterus that ergot is chiefly used. Though attempts have been made to substitute solutions of one or other of these active principles (especially ergotoxine) for preparations of crude ergot, the latter are still commonly used. The most important preparations are the *Extractum Ergotae Liquidum* (B.P.) or *Fluidextractum Ergotae* (U.S.P.) which are given by mouth in doses of about 30 minims, or the

Injectio Ergotae Hypodermica (B.P.) which is injected subcutaneously in doses of 5–10 minims. Those preparations are now tested physiologically (e.g. by determining their activity on the uterus of the guinea-pig) and so standardized. Those preparations are used chiefly for arresting uterine haemorrhage after labour.

XIII

DRUGS WHICH ACT DIRECTLY ON INVOLUNTARY MUSCLE

I. Stimulants

As has already been seen, involuntary muscle can be stimulated to increased contraction by means of drugs which act on the autonomic nervous system; for example, adrenaline constricts the arterioles by stimulating the sympathetic nerve-ends. But many substances stimulate the contractions of smooth muscle by a direct action on the muscle-fibre and independently of the nerve-supply. **Barium** salts act in this way. They stimulate every kind of smooth muscle, e.g. of the blood-vessels, bronchi, gut, ureter, heart, &c. They are, however, of little use therapeutically because they have no selective action, and it is impossible to obtain with barium an action on the smooth muscle of one organ without simultaneously stimulating that of other organs—effects some of which would, in any particular condition, almost certainly be undesirable.

Pituitary.

From a therapeutic point of view the most important member of this group is the extract of pituitary gland. It was discovered in 1895 that this extract raises blood-pressure when injected intravenously. This rise of pressure resembles that produced by extract of suprarenal gland, and it was at first conjectured that both gland extracts might act in the same way. Further researches soon showed, however, that they do not act on the same structures and that, whereas the effect produced by adrenaline on an organ

depends upon the action of the sympathetic nerve to it, the action of pituitary has no relation to nerve-supply but is generally a stimulant one on smooth muscle.

Its action differs, however, from that of barium in being less generalized. A simple chemical compound like a barium salt would be less likely to differentiate between different types of involuntary muscles than an active principle of pituitary gland which no doubt is a complex chemical substance. Whatever the reason, pituitary extract seems to act most strongly on the muscle of the arterioles, uterus, and intestine, and it is for its action on these structures that it is chiefly used.

When pituitary extract is injected intravenously, it produces a rise of blood-pressure which is due to constriction of the arterioles. This pressor effect is more prolonged than that of adrenaline, which it superficially resembles. Pituitary constricts the vessels of an isolated organ when perfused through them. Its action is therefore independent of the vasomotor centre; it acts, like adrenaline, peripherally. The constriction of vessels produced by pituitary bears, however, no relation to their innervation. Thus it constricts the coronary and lung vessels, whereas these, not being supplied with constrictor sympathetic nerves, are unaffected by adrenaline. Pituitary is therefore believed to act directly on the muscle of the vessels. Similarly pituitary has no action on the isolated heart corresponding to sympathetic stimulation; indeed, what slight effect it exerts is in the direction of slowing the heart. Pituitary extract is sometimes used to raise the blood-pressure, where the primary fault is an undue relaxation of arterioles or capillaries; it has no stimulant action on the heart itself comparable to adrenaline.

Pituitary is now widely used to stimulate the contractions of the uterus after labour, especially in prevention or treatment of post-partum haemorrhage. When the placenta separates from the uterus, it leaves the connecting vessels open, and bleeding is stopped in the first instance not so much by contractions of the vessels or clotting inside them as by contraction of the muscle of the uterus itself which occludes the vessels by pressure from without. Here speed of action is imperative, and pituitary, when injected intramuscularly or intravenously, acts almost at once. For this purpose it has gradually supplanted ergot. Pituitary acts directly on the uterine muscle, and stimulates, more or less, the uteri in all animals and in all physiological conditions, thus differing from adrenaline.

Pituitary also to a less degree stimulates the movements of the gut, and is sometimes used for this purpose, especially in conjunction with physostigmine, to arouse the dormant contractions of the gut in cases where these are paralysed after abdominal operations.

When injected intravenously, pituitary usually increases the secretion of urine. In cases of diabetes insipidus, however, it has the opposite effect, diminishing the secretion of urine and relieving thirst. Its action in this disease is only temporary, the effect of one injection lasting only for a few hours.

The part of the pituitary gland which contains the active principle, the actions of which have been described, is the posterior lobe. This active principle has not yet been isolated, so that extracts of the posterior lobe have to be standardized physiologically (e.g. by their effect on a guinea-pig uterus). The preparation usually employed is *Liquor Pituitarii* (U.S.P.), which is given by subcutaneous or intramuscular injection in doses of 2–15 minims.

Histamine, or Ergamine, is an amine obtainable

from the amino-acid histidine in the same way as tyramine is obtained from tyrosine, by splitting off CO_2. It is a substance of great physiological interest, though not of therapeutic importance. It acts very like pituitary on smooth muscle, indeed it was at one time thought that it might even be one of the active principles of pituitary. It therefore contracts the uterus in nearly all animals, and does so in extremely low dilutions.

It produces a fall of blood-pressure in some animals, especially carnivora, and this effect is ascribed to its dilating the capillaries. In this respect—as also in the fact that it produces violent constriction of the bronchi in other animals, especially guinea-pigs—it produces effects similar to anaphylactic shock. Traces of histamine may occur in preparations of ergot (*v.* p. 144).

II. Substances which depress involuntary muscle

As we have seen, there is a variety of ways whereby the tone or rhythmic movements of involuntary muscle can be augmented; in the case of the blood-vessels, for example, by stimulation of the motor centre (strychnine), of the motor nerve-ends (adrenaline), or of the muscle directly (pituitary). Similarly there is a variety of ways whereby the tone or rhythmic movements of smooth muscle can be reduced, e.g. by paralysis of the motor nerve-supply (atropine), by stimulation of the inhibitor supply (adrenaline), or by depression of smooth muscle directly. In regard to the last, though many substances are known which relax smooth muscle as the result of a direct depressing action on muscle-fibres, in the case of most of these this action is accompanied by other undesirable actions. As practical therapeutic

agents, the nitrites, which are now to be considered, occupy a unique position for depressing smooth muscle directly.

In the case of such organs as the bronchi and blood-vessels, which are mere conduits, smooth muscle usually undergoes only changes of tone; whereas in such organs as the heart, alimentary canal, and uterus, which are not merely transmitting channels but also propulsive organs, involuntary muscle has normally the additional property of rhythmic movement. Substances which relax smooth muscle are of importance in treating conditions of undue contraction of smooth muscle which may give rise to either (1) an injurious narrowing of a conduit (e.g. of the bronchi, rendering the air-way too narrow for easy ventilation), or (2) to cramp-like contractions of such involuntary muscle as normally executes rhythmic movement (e.g. of the gut, giving rise to colic).

As has been pointed out before in the case of stimulants of smooth muscle, it is not to be expected that nitrites will act quantitatively alike on smooth muscle in different organs. They act most vigorously on the muscle of the arterioles. They also act definitely on the muscle of the bronchi. They affect chiefly the tone of smooth muscle, and seem to have less effect in inhibiting rhythmic movements. They are therefore chiefly used for widening conduits with smooth-muscle walls.

Amyl Nitrite is a yellow volatile liquid, soluble in alcohol or ether but almost insoluble in water. It has a fruity odour and a pungent taste. It is administered by inhalation. When inhaled, it causes flushing of the skin, at first of the head and neck, but later of the rest of the body. This is due to the dilatation of the arterioles. Larger doses dilate also the arterioles of internal organs. Owing to the relaxation of the vessels there is

a rapid fall of blood-pressure. It often produces a sensation of throbbing in the head. The heart is reflexly quickened by the fall of pressure, but amyl nitrite has no direct effects of importance upon the heart. In the perfused isolated heart, for example, the coronary vessels are dilated by amyl nitrite, but the actual heart-beats are hardly influenced.

This effect on the vessels is due to a direct action of amyl nitrite on their muscle walls. It occurs in perfused isolated organs, where any action on the vasomotor centre is of course excluded. Amyl nitrite has a somewhat similar action on other forms of smooth muscle, especially on that of the bronchi.

The physiological activity of amyl nitrite is due mainly to the nitrite part of the molecule, and a similar action is exerted by many *other nitrites* (e.g. sodium nitrite) in which the group O . NO is found. Inorganic nitrates (like sodium nitrate) which have the group $O . NO_2$ do not possess this action, but certain *nitric esters* such as glycerine trinitrate are partly reduced in the body into nitrites and have an action similar to nitrites. These nitric esters are therefore conveniently included in the group of nitrites. The official members of this group are amyl nitrite, sodium nitrite, ethyl nitrite, glycerine trinitrate (nitroglycerine), and erythrol tetranitrate. These all similarly relax smooth muscle but differ from one another chiefly in regard to the speed and duration of action. These time-differences are of importance in determining the suitability of each for particular conditions.

Therapeutic uses of Nitrites and Nitric Esters. Amyl nitrite acts very rapidly, but its action is over in a few minutes. It was introduced by Brunton for the relief of angina pectoris, a cardiac attack characterized by sudden onset, great pain, and sometimes by a rise of blood-pressure. Its beneficial effect in this condition

is believed to be due largely to its dilating the coronary vessels. In angina pectoris the remedy is required at once, and for convenience and for accuracy of dose, amyl nitrite is usually put up in glass capsules which can be broken in a handkerchief and the nitrite inhaled. It is sometimes similarly given in asthma, which it relieves by relaxing the spasmodically-constricted bronchi. Large doses of amyl nitrite tend to produce methaemoglobin in the blood.

Sodium Nitrite acts similarly. It is a crystalline solid and given by mouth. It therefore takes longer to act, but the effect is more lasting. The nitric esters are still slower in action. *Nitroglycerine* and *erythrol tetranitrate* are used to lower an unduly high blood-pressure. The effect, especially of the latter, is prolonged for several hours.

Preparations. Amyl Nitris, 2–5 minims by inhalation. Sodii Nitris, $\frac{1}{2}$–2 grains in solution or tablets. *Spiritus Aetheris Nitrosi*, 4 per cent. ethyl nitrite in alcohol, 15–60 minims.

Tabellae Trinitrini, $\frac{1}{130}$ grain of nitroglycerine in each, 1–2 tablets. *Liquor Trinitrini* (B.P.), *Spiritus Glycerylis Nitratis* (U.S.P.), a 1 per cent. alcoholic solution of nitroglycerine, $\frac{1}{2}$–2 minims. *Erythrol Tetranitrate*, $\frac{1}{4}$–1 grain, in alcoholic solution or tablets.

XIV

DRUGS ACTING ON HEART-MUSCLE: CARDIAC TONICS

We have had numerous examples of drugs which influence the tone or rhythmic contractions of smooth muscle, either in the direction of stimulation or of depression, and produce their effects either on the muscle directly or through the mediation of the nerve supply. We have also seen that most drugs exercise some selective action on smooth muscle; for example, pituitary stimulates the muscle of the uterus to a much greater extent than that of the bronchi, and nitrites have a more powerful dilating effect on the muscle of the arterioles than on the smooth muscle of most other organs. It is not surprising, therefore, that when we come to a type of involuntary muscle like the heart, which has diverged very considerably from the usual type of smooth muscle, this selective action will be even more apparent. For example, pituitary and nitrites have hardly any direct effect on heart-muscle at all. Conversely it would be reasonable to expect that some drugs would influence the contractions of the heart, while having relatively little effect on other forms of involuntary muscle, and this is true of one very important group of therapeutic agents, sometimes called the cardiac tonics, which, at least in the case of smaller doses, have a powerful action on the heart while exercising little action on other forms of involuntary muscle. To this group belongs a large number of plants whose active principles all have a very similar qualitative effect on the heart. In the case of all these plants the active principles have been found to be glucosides. Of this group only the three

members which are in official use need be considered. They are digitalis, strophanthus, and squill. Of these three, digitalis is the most important and will be considered first.

Digitalis.

Digitalis, the leaves of the foxglove, *Digitalis purpurea*, was introduced into regular medicine by the distinguished physician and scientist, William Withering, who in 1785 published a book advocating its use as a diuretic, based upon a clinical experience extending over the previous ten years. It was not fully realized until long afterwards that this diuretic effect produced by digitalis is the result of an improvement in the blood-supply of the kidney and consequent upon an action of the digitalis not upon the kidney directly but upon the heart. Digitalis has gradually attained a place of the first importance in the treatment of diseases of the heart.

Action on the Heart. The full story of the actions of digitalis on the heart cannot be told here. The actions differ according to the species of animal, and in the same animal under different conditions of cardiac disease. Here it is only possible to give an elementary account of those actions in so far as they subserve the therapeutic uses of digitalis in man. It has been known for half a century or more that, in many cases of cardiac disease accompanied by undue rapidity and by irregularity of the heart-beats, digitalis can slow the pulse, improve the circulation, and remove symptoms, such as oedema, defective secretion of urine, &c., which are the result of the impairment of the circulation. Especially in the last twenty years, a large number of researches have been devoted to obtaining a more precise delimitation of the varieties of cardiac disease in which digitalis can be effectively employed

and towards a more accurate explanation of its method of action.

Digitalis in the first place increases the force of the contraction of the heart. In the initial stage this is shown by a slight increase and prolongation of ventricular systole. If the concentration be increased, the systole is prolonged and the relaxation diminished until the heart stops in systole. This effect is produced both in cold- and in warm-blooded animals, and is the most characteristic action of the glucosides of the digitalis group. This action is readily seen in the perfused isolated heart.

The slowing of the heart by digitalis may be brought about in different ways. In the normal heart it is mainly due to stimulation of the vagus centre. Thus in the mammal it does not occur in the normal perfused isolated heart and in the intact animal is prevented by atropine. A supplementary and important cause of the slowing produced by digitalis in cardiac disease has more recently been emphasized. In the condition known as Auricular Fibrillation, digitalis may slow the heart in spite of the simultaneous administration of atropine; in this case the slowing cannot be due to stimulation of the vagus centre, for atropine would prevent these stimuli reaching the heart. It has been found that in auricular fibrillation digitalis slows the pulse by diminishing the conductivity of the auriculo-ventricular bundle. When the auricle is fibrillating, the ventricle is bombarded by rapid feeble impulses from the auricle, and responds by beating as fast as it can, and the beats have no regularity. Digitalis by this second action prevents a great number of these impulses from reaching the ventricle and so the heart-rate is slowed, though the fibrillation of the auricle is not necessarily, or usually, stopped by digitalis.

In cases of heart disease when the heart is beating

very rapidly and irregularly, the output of the heart per unit of time is diminished. This is so because the diastolic pause is of too short duration to enable the heart to fill completely, and also because usually the contraction is too feeble to expel completely even this limited quantity of blood. By prolonging the diastolic pause digitalis allows the heart to fill more completely, and by augmenting the force of systole it enables the heart to empty itself more completely. The output per unit of time is increased in spite of the slowing, and the velocity of the peripheral circulation can be shown to be greater. More blood is driven into the arteries and the congestion of the veins is relieved. The condition of the heart itself is improved by the increase in its own blood- (and therefore oxygen-) supply.

All organs of the body suffer if the circulation is defective. This is conspicuously so in the case of the kidney. In many cases of heart disease there may be, owing to impairment of the blood-flow through the kidney, a marked diminution in the secretion of urine and widespread oedema of the body. In these cases digitalis, by improving the circulation through the kidney, often produces an enormous increase in the flow of urine and a rapid removal of the oedema. It was for this diuretic effect that Withering first used it. It must be remembered that this diuretic action is not a direct one on the kidney. It does not occur, for example, in animals with a normal circulation. It is an effect secondary to improvement of the circulation where that is defective.

This increase in the output of the heart is by far the most important action of digitalis, and indeed, in small doses, almost its only action. Higher concentrations than are required to produce a therapeutic effect on the heart may act on involuntary muscle in other organs; for example on the muscle of the arterioles or

uterus: but these effects are not produced by medicinal doses of digitalis in man.

The digitalis glucosides are irritating substances and may produce nausea and vomiting, both by irritation of the stomach as well as by an action on the vomiting centre which, like the cardiac vagus centre, they stimulate. The glucosides are slowly absorbed from the alimentary canal, so that, when given in the ordinary way by mouth, digitalis usually takes two or three days to produce its full effect. They are also slowly eliminated, so that, once the effect on the heart is produced, it usually persists for several days after digitalis is discontinued. The rate of elimination may be even slower than that of absorption, so that, if given continuously, digitalis may accumulate in the body and its action go beyond what is intended or desirable. One symptom of overdosage produced in this way is an undue slowing of the heart. The rate of beat may be so low as thirty per minute.

Active Principles and Preparations of Digitalis. The glucosidal active principles of digitalis are unstable and difficult to isolate pure. The most important of these are *digitoxin*, soluble in alcohol but not in water, and *digitalein* (gitalin), soluble both in alcohol and in water. The tincture therefore contains both, and is the best preparation for general use. There is also in the digitalis leaves a saponin, digitonin, which does not have the cardiac actions of the other two. It is of importance, however, because it helps to keep the digitoxin in solution in water and thus explains the presence of small quantities of digitoxin even in a watery preparation like the infusion. This saponin also facilitates the absorption of the real active principles from the alimentary canal.

The dose of powdered digitalis leaf is 1–2 grains. Of its two preparations, *Tinctura Digitalis*, 5–15

minims or more, is more commonly used; less frequently *Infusum Digitalis*, 2–4 fluid drachms (an exceptionally small dose for an infusion).

When the tincture of digitalis is given in ordinary doses (e.g. 10–15 min. three times a day) it may take 2–5 days before the heart is fully under its influence. In cases of urgency and especially where a patient is under continual observation, much larger doses may be given at first, so as to obtain a digitalis effect in 12–24 hours. To attain this end different arrangements of dosage have been tried. One method is to give 90 minims, followed in 6 hours by 60 minims, and again in 6 hours by 30 minims, after which normal doses may be given as required. To get the full benefit from the cardiac tonics, accurate dosage is necessary. This can be attained only if the preparation used is of constant and known physiological activity. As the amount of active principles in varying samples of leaf is not constant, the amount in tinctures, even if always prepared according to the same formula, will vary correspondingly. As there is no known convenient method of chemically assaying preparations of digitalis, these have to be standardized by some physiological test. According to one such test, a certain minimum dose injected into the lymph-sac of a frog of given weight must produce systolic arrest of the ventricles in one hour. The tincture can, for example, be made in the first place more concentrated than necessary and subsequently diluted with alcohol until the required degree of activity is reached. The same method of physiological standardization is applied to preparations of strophanthus and squill.

Strophanthus.

The seeds of various species of Strophanthus have been used by natives of Africa for the preparation of

arrow-poisons. These arrow-poisons were investigated, about half a century ago, by Fraser, who found that strophanthus had actions on the heart similar to those of digitalis and recommended it as a substitute for the latter in the treatment of heart disease.

The pharmacological actions and therapeutic applications of strophanthus are so similar to those of digitalis that they need not be recapitulated. Certain minor differences between them need mention. The active principles of strophanthus seem to be more easily destroyed in the alimentary canal than those of digitalis, and the amount of them absorbed is less constant. Moreover, the difference between the therapeutic and the toxic dose seems to be less with strophanthus than with digitalis. The dosage of the former has therefore to be watched more carefully. Consequently, for oral administration, digitalis is usually and deservedly preferred to strophanthus. On the other hand, cases which are unusually intolerant of digitalis, or which fail to respond to it, may fare better on strophanthus. Strophanthus is usually given as *Tinctura Strophanthi*, 2–5 minims (B.P.), 8 minims (U.S.P.).

From strophanthus can be prepared a crystalline active principle, *Strophanthinum*, which is soluble in water. This can be given intravenously and is sometimes so used when a rapid action on the heart is necessary. As strophanthin is a very powerful poison in overdosage, great caution is needed with regard to dose and rate of injection. A usual intravenous dose is $\frac{1}{200}$ grain. None of the active principles of digitalis is equally suitable for intravenous injection.

Squill.

Squill (*scilla*) is one of the oldest of medicines and was well known to the ancient Greek physicians.

Preparations of squill have long been used as emetics, expectorants, and diuretics, and within the last half-century it has been found that the active principles of squill are glucosides, difficult to isolate, which act in the same way as those of digitalis and strophanthus. Compared with the latter, squill is more irritant to the stomach, and in early days was frequently used as an emetic. The expectorant action of it is secondary to this, but, in cases of cardiac bronchitis, may be also due to improvement of the circulation in the lung resulting from the action of squill on the heart. Squill seems to be less perfectly absorbed than digitalis, and is therefore less suitable for general use in cardiac disease. It is chiefly used as an expectorant and, as an adjuvant to digitalis or other remedies, as a diuretic. There are several official preparations, of which *Tinctura Scillae*, 5–15 minims, is one of the best.

XV

DRUGS WHICH INFLUENCE METABOLISM

Thyroid Gland.

The internal secretion of the thyroid gland is essential for normal development and health, as is shown by the remarkable effects resulting from deficiency of it. Congenital deficiency (cretinism) arrests and warps development, affecting probably all organs more or less, but conspicuously the skeletal structures, the integument, the nervous system, and metabolism. The child is dwarfed, with thick dry skin, coarse hair, and protuberant abdomen. Mental and sexual development is retarded and the basal metabolism is low.

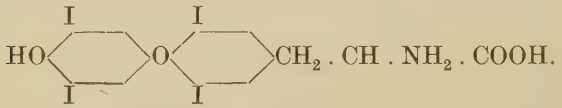
In deficiency of thyroid secretion in adults, either from pathological causes (myxoedema) or as the result of operative removal of the thyroid gland, the effects are very similar, except that growth has been complete before the deficiency comes on.

In such conditions, more or less complete recovery may result from thyroid administration. In cretinism the earlier the treatment is begun the better are the results, and administration of thyroid must be continued during life. The exact dose necessary to maintain normal metabolism must be determined for each case. Thyroid administration is also useful in less severe forms of thyroid deficiency. The decrease in weight and rise in basal metabolism resulting from thyroid medication has suggested its use in obesity, which it sometimes temporarily reduces. Overdosage with thyroid produces symptoms similar to those seen in Graves's disease (exophthalmic goitre), e.g. sweating, rapid pulse, tremors, and loss of weight.

The preparation commonly used is *Thyroideum*

Siccum ($\frac{1}{2}$–4 gr. by mouth). This is a light brown powder prepared from the fresh thyroid gland of the sheep, with the fat removed.

The active principle of the thyroid gland, called *thyroxin*, has recently been isolated and synthesized. It contains iodine and has the following constitution



As the activity of the dried gland depends upon the amount of thyroxin present in it, some measure of this activity can be obtained by determination of the iodine content of the dried gland. It must contain 0·2 per cent. of iodine in thyroid combination.

Thyroxin itself forms white crystalline needles, insoluble in water but soluble in strong alkalis. It seems to produce the same results as the dried gland, though the latter acts better by mouth. The dose of thyroxin is 0·2 to 2·0 mg. In excess it is of course a powerful poison.

The thyroid gland contains a much higher concentration of iodine than the other tissues of the body, and the iodine necessary for the continual manufacture of thyroxin is obtained from the food. Though the actual amount of iodine necessary in the food is very small, in some regions even this minute amount is wanting, and there goitre is endemic. In such districts the administration of small quantities of iodides to children improves their growth and development, and diminishes the incidence of goitre.

Parathyroid Gland.

Complete removal of the parathyroid glands causes death in a few days owing to lack of a hormone necessary to life, which these glands secrete into the blood. Among the effects resulting from removal of the

parathyroids is a lowering of the blood-calcium, with a consequent increase in muscular irritability giving rise to tetany. Though the chemical nature of this hormone is not yet known, a powerful extract of the gland can be prepared which contains it, and which, when injected, causes a rapid rise in the serum calcium and relieves tetany if present. Parathyroid extract increases the blood-calcium by withdrawing calcium from the bones or soft tissues, not by increasing its absorption. It produces therefore only a temporary effect. It has been used tentatively in a number of pathological conditions, but especially in tetany.

Iodides.

Iodides have been used in the treatment of many diseases, in some of which no complete explanation can yet be given of their method of action. It is not quite satisfactory, therefore, to include them in any group of remedies. Seeing, however, that in two important therapeutic uses—in thyroid diseases and in syphilis—the action of iodides can fairly be described as an action on metabolism, iodides can perhaps most conveniently be taken here.

The salt most commonly used medicinally is iodide of potassium, but the actions to be described occur equally well with sodium iodide or indeed with any compound which will liberate the iodide ion.

Potassium iodide forms colourless crystals which have a pungent and somewhat bitter salt taste and are freely soluble in water. Large doses, especially if concentrated, irritate the stomach and may produce nausea and vomiting, but this rarely occurs from medicinal use. Iodides are absorbed very rapidly from the alimentary canal and, in their subsequent distribution and excretion, generally resemble chlorides and bromides. Of a single dose, therefore, the

greater part is rapidly excreted, chiefly in the urine, but also in other secretions such as saliva and milk; while a diminishing part may be retained in the body for some days. A slight diuretic effect may occur from salt action (p. 22), but iodides do not seem to have any specific action on the kidneys.

People vary very much in their sensitiveness to potassium iodide, so much so that it is impossible to describe certain effects as regularly occurring after certain doses. It was found that when repeated doses of iodides were given, certain disagreeable symptoms might appear to which collectively the name *Iodism* was given. Occasionally this may occur after a single dose, and in any case the amount of iodide which can be given before symptoms of iodism appear varies widely in different individuals. The commonest symptoms of iodism are swelling and catarrh of the mucous membrane of the respiratory tract, usually accompanied by a profuse watery secretion. This is shown by swelling of the mucous membrane of the nose, with sneezing and increased secretion. There may be also conjunctivitis, and catarrh of the frontal sinuses with headache. Less commonly laryngitis, tracheitis, or bronchitis may occur. Various kinds of skin eruptions may also appear, most frequently of an erythematous or papular type. These effects are probably connected with the excretion of iodides by the various surfaces involved.

While these symptoms are to be avoided as far as possible, iodides are frequently administered to produce a minor degree of one of the symptoms, namely an increased secretion from the trachea and bronchi. In cases of bronchitis, where it is desirable to increase the quantity and diminish the viscidity of the bronchial secretion, potassium iodide is a reliable and valuable expectorant.

As has already been mentioned, iodine is an essential constituent of thyroxin, the active principle of the thyroid gland. It is therefore not surprising that overdoses of iodides may occasionally produce symptoms due to excessive secretion of thyroxin, i.e. symptoms similar to those of Graves's Disease. Iodides may also relieve symptoms of thyroid deficiency, and are especially important in the prophylaxis of such diseases (p. 162).

Perhaps the most important therapeutic use of potassium iodide is, however, in the treatment of syphilis. It is of value only in the later stages of this disease, especially when ulcers or gummata are present. The fact that it has no remedial effect in early syphilis renders it improbable that it can act by killing the spirochaete. Indeed, everything goes to show that it does not act like mercury, bismuth, or arsenic as a parasiticide. It acts on tissues, in some way not understood, dissolving and removing gummatous tumours. Iodides are also useful in actinomycosis, and sometimes in chronic rheumatism.

Potassii Iodidum (B.P., U.S.P.) or *Sodii Iodidum* (B.P., U.S.P.) are given in doses of 5 grains or less as expectorants, and 5–20 grains in the treatment of tertiary syphilis. In actinomycosis much larger doses are often given.

Phenylquinoline carbonic acid or **Cinchophen** (U.S.P.), introduced under the name of Atophan, has a remarkable effect on the kidney in rendering it permeable to uric acid. Atophan increases the amount of uric acid in the urine while causing temporarily a corresponding fall in the concentration in the blood. This increased excretion of uric acid seems to improve some cases of gout, in which disease urates are unduly retained. Like many aromatic substances, atophan has also an antipyretic and analgesic action. It is a

colourless crystalline powder, with a bitter taste, and almost insoluble in water. In gout it may be given in doses of 30 grains a day, in divided doses, as a powder or in tablets.

Colchicine.

Preparations made from the corm or seeds of *Colchicum Autumnale*, a plant which grows in meadows and pastures over large areas of Europe and N. Africa, have been used since the Middle Ages as a remedy for gout. The chief active principles of the plant is an alkaloid colchicine (*Colchicina* (U.S.P.) $\frac{1}{120}$ gr.).

Colchicine is an intense local irritant. It is excreted by the intestines and by the kidney and, when given in large doses, produces an inflammatory irritation of these organs, with resultant nausea, vomiting, and diarrhoea, and sometimes anuria. Medicinal doses ought not to produce effects other than nausea or slight purging. The action of colchicum is interesting in that it produces effects only after a latent period of several hours, an interval which is not shortened by increasing the dose. Colchicum also has an action like pilocarpine on smooth muscle, and causes an increased leucocytosis after a temporary leucopenia.

None of its actions can at the present time explain its beneficial action in gout. In acute cases of this disease it relieves the pain in the joints, but seems to have little effect in preventing subsequent attacks. It may be given in the form of *Tinctura Colchici* (5–15 min. B.P., 30 min. U.S.P.).

Vitamins

Vitamins are substances occurring in various articles of diet and necessary for insuring normal development and maintaining health, but which act in such small quantities that they cannot be regarded merely,

if at all, as sources of energy. They seem to act somewhat like thyroxin in the sense that they control the development and stability of organs. A number of vitamins have already been recognized by the effects resulting from their absence in foods or from the positive effects occurring when the deficiency is supplied, but, with one doubtful exception, little is known of their chemical composition. In the meantime they have been given merely alphabetical characters to distinguish them. Here it will be possible only to mention those in regard to whose existence there is most certainty.

Vitamin A is soluble in fats and oils and generally occurs in association with some animal fats, such as cod-liver oil or butter, but is absent from vegetable oils like olive oil. It is necessary for growth of young animals. In its absence animals develop also abnormalities of endothelial or epithelial structures (e.g. xerophthalmia) with a liability to various infections especially of these surfaces. The most convenient medicinal source of this vitamin is Cod-Liver Oil.

Vitamin B (antineuritic vitamin) is soluble in water and alcohol but insoluble in fats and oils, and is found in most forms of plant life but especially in germinating seeds and yeast. If it is withheld from the diet, its absence causes especially a polyneuritis (Beri-beri in man), and this disease is rapidly cured when the vitamin is supplied.

Vitamin C (antiscorbutic vitamin) is soluble in water and alcohol and is abundant in growing vegetables, especially citrous fruits and tomatoes. Malnutrition and scurvy result from lack of this vitamin in the diet, and are cured when it is adequately supplied. Lemon or orange juice is a convenient source of it.

Vitamin D (antirachitic vitamin) is, like Vitamin A, found especially in animal fats. Its importance lies

in its efficacy to prevent or cure rickets. Sterols, especially ergosterol found in yeast, when suitably exposed to ultra-violet rays, acquire potent anti-rachitic properties, but whether a sterol so irradiated is to be regarded as the ultimate Vitamin D is not yet certain. Exposure of the skin to direct sunlight or ultra-violet rays may also cure children of rickets, possibly by activating sterols in the skin. Cod-liver oil is a convenient source of this vitamin, but irradiated sterols are now also prepared for the treatment or prevention of rickets.

Cod-Liver Oil, *Oleum Morrhuae*, is a fixed oil extracted from the fresh liver of the cod (*Gadus morrhua*). It has a pale yellow colour and a slight but rather disagreeable odour. It is an easily absorbable fat and is therefore a valuable food, and has long been used, mainly from this point of view, in malnutrition and wasting diseases such as tuberculosis. It has acquired a new importance in recent years from its high vitamin content, especially of Vitamins A and D. When given in small doses in rickets it produces a remarkable improvement. Growth is accelerated, calcification of the bones and teeth is improved, and probably resistance to certain infections is increased. A usual dose is from $\frac{1}{2}$–1 teaspoonful.

Insulin.

Insulin is a preparation made from the pancreas and containing the active hormone of the islets of the gland, whence its name. It was shown, about forty years ago, that removal of the pancreas in animals produced symptoms similar to those of diabetes mellitus in man; and, about twenty years ago, that these symptoms could be prevented by pancreatic grafts. It was not until 1922, however, that Banting and Best were successful in obtaining from the pancreas an active pre-

paration containing the hormone in a state of sufficient purity to be used in diabetic patients. To this preparation they gave the name Insulin.

Insulin is destroyed by pepsin and trypsin, and has no action when given by mouth. When injected subcutaneously, insulin causes a fall in blood-sugar, the degree of fall depending upon the dose administered. This effect is produced in normal animals and in diabetic patients, and is due to the fact that insulin increases the capacity of the tissues to take up and metabolize sugar. In diabetes mellitus this capacity is partly or wholly lost, due to lack of the normal internal secretion of the islets of Langerhans. Administration of insulin supplies this defect, and must be regulated according to the severity of the diabetes. Insulin therapy of diabetes, therefore, is analogous to thyroid treatment of myxoedema. It is not a permanent cure and, unless the pancreas recovers its normal power of secreting the hormone, insulin must be given more or less continuously, as may be necessary.

The chemical composition of insulin is not yet known, though Abel has obtained a very active crystalline substance which he believes to be the active principle. In the meantime the activity of insulin is determined physiologically in terms of 'units'. A unit for medicinal use is one-third of the amount of insulin which, injected hypodermically in a rabbit weighing about two kilogrammes, will reduce the blood-sugar to 0·04 per cent. (i.e. about one-fourth of the normal) in 2 hours. In diabetes daily doses of 5–40 units or even more may be given, depending upon the severity of the disease and the amount of carbohydrate allowed in the diet.

If too much insulin is given, symptoms of 'hypoglycaemia' occur. The normal amount of glucose in

the blood is about 100 mg. per 100 cc. If the blood-sugar is reduced to below two-thirds of this amount, symptoms such as sweating, faintness, tremulousness, and a feeling of anxiety may come on. If the sugar is reduced to 50 mg. per 100 cc., aphasia, delirium, or even coma and death may ensue. Diabetics vary considerably in regard to the toxic symptoms induced by a given degree of hypoglycaemia. Symptoms of hypoglycaemia can be rapidly relieved by the administration of sugar by mouth or, if necessary, by vein; or adrenaline can be used in emergency, as it causes hyperglycaemia.

Given in correct dosage, insulin causes a remarkable alleviation of the symptoms of diabetes. Accompanying the fall in the sugar of the blood, there is diminished glycosuria, polyuria, and thirst; and, with the aid of insulin and suitable diet, many diabetics can resume active physical and mental work.

XVI

PHENOL AND ALLIED AROMATIC COMPOUNDS

Benzol.

The vapour of benzol when inhaled may cause a kind of intoxication or, if the quantity be large enough, fatal poisoning. Concentrated vapour may cause rapid death. The chief interest of it in this connexion is from its wide industrial use, when it may give rise to poisoning, usually chronic. Of the effects it produces, one of the most characteristic is an injury of the blood-forming organs, leading to a marked diminution of the leucocytes in the blood, especially of the polymorphs. This action has led to its therapeutic use in small doses in leucaemia to reduce the number of leucocytes, and it has been found to have a remedial value in some—especially early—cases of the disease, and even to cause diminution in the size of the spleen. It has usually to be given for some weeks in doses of 5 rising to 15 minims, after meals to avoid irritation of the stomach. Benzol is partly oxidized in the body to phenol and excreted like it, but most of it is excreted unchanged by the lungs.

Numerous derivatives of benzol are used in medicine either for their local actions as antiseptics or for their actions as analgesics or antipyretics. Benzol itself, C_6H_6, is not so active as many of its derivatives, partly because of its insolubility, but chiefly from the difficulty with which it combines with protoplasm; but relatively slight changes in its composition may produce a great increase in its physiological activity, such as the substitution of -OH for H, forming phenol. The benzene ring itself is not easily decomposed in the body, and for the most part passes through it unchanged,

though the organism does possess the power of destroying the benzene ring of those aromatic amino-acids which enter into the composition of proteins. Foreign aromatic compounds require to be rendered innocuous by being combined with sulphuric acid to form aromatic sulphates, or with glycocoll to form acids of the type of hippuric acid. The few exceptions are compounds which so closely resemble the protein fractions in their structure that they fall victims with these to the normal destructive processes.

Phenol.

Carbolic acid C_6H_5OH was the first substance intentionally used as an antiseptic, its earliest use by Lister dating back to 1867. The presence of the hydroxyl group renders phenol more soluble than benzol and more reactive with protoplasm. Phenol forms a loose combination with proteins and is also more soluble in lipoids than in water, so that it readily penetrates cells. It is a general protoplasmic poison, killing all living cells if in sufficient concentration.

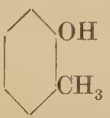
External Actions. Concentrated carbolic acid is a powerful caustic. Solutions even so dilute as 2 per cent., if applied to the skin and prevented from evaporating, may cause local gangrene. This occurs most readily in the case of the fingers. The epidermis becomes at first white, wrinkled, and opaque, and at least partly anaesthetic, and later necrotic. It is therefore dangerous to keep a wet phenol dressing on the fingers, as local gangrene may occur even within 24 hours. As an antiseptic, phenol has now been largely superseded. It is irritant to wounds or mucous membranes in the concentrations needed to inhibit bacterial growth, and it is fairly easily absorbed from any absorbing surface, and thus may produce general poisoning. Its ready absorbability renders it useless as

an intestinal antiseptic, though it is occasionally used as a stomach antiseptic. Its most common use now is to keep instruments sterile.

Actions after Absorption. Phenol is readily absorbed. It is not now used therapeutically for any action that it can exert after absorption, but poisoning with it is not uncommon, so that a brief reference to the effects of large doses is needed. It has no high degree of selective action, so that most tissues are more or less injured by it. The central nervous system is markedly affected, being depressed, with or without a previous stage of excitation. Especially with large poisonous doses in man, coma and death may occur in less than an hour, with no preceding convulsive stage. There is usually a rapid fall of temperature. Respiratory failure is the main cause of death, but the heart and vasomotor centre are also depressed.

Carbolic acid is excreted in the urine partly as such and partly oxidized to dioxy- compounds. All these compounds are excreted in combination with either sulphuric or glycuronic acid. The presence of these compounds may give to the urine a smoky colour, which darkens further on standing, owing to further oxidation.

The entrance of Alkyl groups into the nucleus diminishes the general toxicity without proportionately diminishing the antiseptic power, e.g. in the *cresols*



Owing to this, substances of the cresol type have largely replaced phenol itself as antiseptics, because an equal antiseptic action can be obtained by them with greater safety. But this introduction of an

alkyl group, while diminishing the toxicity, has the disadvantage that it diminishes also the solubility. They are in fact not sufficiently soluble to be used as surgical antiseptics in simple solution, but have to be emulsified in some way. Preparations like *creolin* and *lysol*, which are widely used as surgical antiseptics, are mixtures of the three isomeric cresols emulsified in different ways; e.g. in the case of creolin by means of hard soap, or in the case of lysol by means of soft soap.

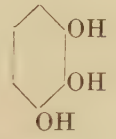
Guaiacol, $C_6H_4 . OCH_3 . OH$, and the **Creosols,** $C_6H_3 . CH_3 . OCH_3 . OH$, have a very similar action to the cresols and phenol. Guaiacol, especially in the form of guaiacol carbonate (5–15 gr.) has been given internally in phthisis and bronchial diseases with the idea of restraining the growth of organisms in the lungs and bronchi. It is more than doubtful whether the concentration of guaiacol that is attained in the lungs is sufficient for this purpose.

The substances of the foregoing group, including phenol itself, can be obtained by fractional distillation of coal-tar or wood-tar, or can be made synthetically. Wood-tar (*Pix Liquida*) and prepared coal-tar (*Pix Carbonis Praeparata*) contain a variety of phenol derivatives and are sometimes used as antiseptics, especially for the skin.

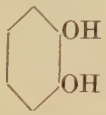
Creosote, which is made from wood-tar by distillation (whereby many of the more poisonous constituents are eliminated), consists mainly of creosols and guaiacols. It resembles them in action. Creosote has been used internally, like guaiacol itself, in the treatment of phthisis and other infective pulmonary diseases, but its value in these conditions is disputed.

In the foregoing paragraphs, the modifications in the action of phenol brought about by the introduction of alkyl groups have been considered. Brief reference must now be made to the introduction of

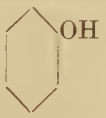
hydroxyl groups. As already pointed out, the entrance of a hydroxyl group into the benzene nucleus makes it more soluble and physiologically more active than benzene itself. The addition of further hydroxyl groups makes the resulting substance still more toxic; e.g. pyrogallol



is more toxic than catechol



which in turn is more toxic than phenol



The dioxybenzols—pyrocatechin, resorcin, and hydroquinone—generally resemble phenol in action but are more poisonous.

Resorcin is sometimes used in ointments for skin diseases. One of the trioxybenzols, **pyrogallol,** is still more poisonous but is also occasionally used in the same way.

Volatile Oils.

Many other aromatic compounds, more or less closely resembling phenol in constitution and action, have been used medicinally. One group of these, which resembles phenol fairly closely, is that of the volatile or essential oils. They are aromatic com-

pounds and have no chemical relation to the fixed oils, which they resemble only in their solubilities. They can be distilled unchanged and are usually obtained from plants by distillation, whereas a fixed oil so treated splits into its two components, glycerine and a fatty acid.

The characteristic odour of plants is generally due to the presence, in the flower or elsewhere, of a volatile oil. Volatile oils are, therefore, very widely distributed in the vegetable kingdom, and, as plants containing them would often attract attention from their pleasant smell, a very large number of such plants have come into culinary and medicinal use, owing such action as they have almost entirely to the volatile oil in them. To this unwieldy heritage, only a brief reference can be made here.

While the volatile oils differ from one another in composition, as a result of which they differ in smell and, to some extent, in pharmacological action, they nevertheless have a generic resemblance in chemical structure and in action.

Most of them are of the nature of terpenes having the formula $C_{10}H_{16}$. They are usually just sufficiently soluble (of the order 1 in 5,000) in water to impart their odour to it. They are antiseptics, but too insoluble and too expensive for general use. They usually irritate the skin in concentration, especially if evaporation be prevented, but after the preliminary irritation some of them produce partial local anaesthesia like phenol.

Taken internally, they stimulate appetite, especially if the odour is agreeable. They aid in the expulsion of gas from the stomach and tend to prevent colic, apparently by suppressing excessive contractions of the gut. In medicinal doses they have little action while circulating in the blood. They are excreted in

the urine, usually combined with glycuronic acid, or in the lungs unchanged, and especially in the former exert a mild antiseptic action. Like a great many mild irritants they increase the secretion of urine while passing through the kidney.

Larger doses affect chiefly the central nervous system, and here the actions of individual oils vary. Usually they depress the central nervous system eventually, but some of them, e.g. absinthe, first stimulate the cerebral centres and may even produce convulsions. Their action on the central nervous system is therefore not unlike that of phenol.

It remains here only to mention which particular oils have come to be used for the various actions that they all exert more or less.

1. Flavouring agents. Of these **peppermint, cinnamon, anise,** and **caraway** may be mentioned. The usual dose of the pure oils is $\frac{1}{2}$–3 minims. All of them have, as an official preparation, an Aqua, which is practically a solution of the oil in water and is used mainly as a vehicle for mixtures in doses of $\frac{1}{2}$–1 fluid ounce, e.g. *Aqua Menthae Piperitae*, peppermint water.

2. Some are used as counter-irritants, e.g. **oil of turpentine** in the form of *Linimentum Terebinthinae*, or **cayenne pepper** in the form of *Unguentum Capsici* (*v.* p. 114).

3. Many of them can be used as carminatives, and they are very commonly used to prevent griping. Many of the official purgative and astringent pills and powders contain a volatile oil to prevent colic. In the purgative preparations the volatile oil prevents the colic which might be set up by the purgative which is being prescribed; in the astringent preparations, it prevents the colic which is an accompaniment of the diarrhoea that is being treated. The household use of

dill water, *Aqua Anethi*, for the relief of griping in infants, may be mentioned.

4. One of the preparations most commonly used as external antiseptics is *Unguentum Eucalypti*. Oil of Eucalyptus is sometimes also used as a bronchial antiseptic in the same way as creosote, mentioned in the preceding section.

5. As urinary antiseptics *Oleum Copaibae*, *Oleum Santali* (oil of sandalwood), and *Oleum Cubebae* are all used in doses of 5–20 minims. These used to be prescribed very commonly in gonorrhoeal urethritis, and they do exercise some antiseptic action in the urine, but more reliance is now placed in the use of local antiseptics for these conditions.

6. Probably all of the volatile oils exert some diuretic action, but the only one that is used specifically for this purpose is the *Oil of Juniper*. The superiority of Gin, which is flavoured with Oil of Juniper, as a diuretic over other alcoholic beverages has been long recognized.

Stearoptenes.

Under certain circumstances crystalline substances separate out from the volatile oils. Three of these, thymol, camphor, and menthol, called Stearoptenes and containing oxygen in their molecule, are of considerable medicinal importance. Chemically and pharmacologically they very closely resemble the volatile oils proper.

Thymol is a powerful antiseptic used chiefly for the nose and mouth. Its chief importance is as a remedy for hook-worm (*v.* p. 212).

Camphor is a less efficient antiseptic. Locally it is used chiefly as a counter-irritant (*v.* p. 114) in the form of *Linimentum Camphorae* (camphorated oil), a solution of 1 part camphor, 5 of olive oil. Camphor has

long been used in the East as a 'stimulant'. Taken internally it produces a sensation of warmth in the stomach, such as is produced by other gastric irritants like alcohol or mustard. Larger doses stimulate the central nervous system, and may produce restlessness, excitement, delirium, and even epileptiform convulsions. Those effects are not of course produced by medicinal doses, but they may afford some explanation for the use, especially in the East, of camphor as a stimulant and aphrodisiac.

Especially on the Continent, camphor has been widely used as a stimulant to the circulation. Clinical evidence of its value is conflicting. It does not seem to have any direct action on the heart. It is usually given hypodermically or intramuscularly dissolved in a fixed oil. Any beneficial effect that it may produce in certain cases may be due to its irritation of sensory nerves causing reflex stimulation of the vasomotor centre.

Menthol generally resembles thymol and camphor in action. It is more interesting than important. If rubbed into the skin, it produces a local sensation of cold followed by partial local anaesthesia. The sensation of cold is supposed to be due to stimulation of the terminations of the nerves that convey the sensation of cold, and the anaesthesia to paralysis of the touch and pain nerves. Almost the only medicinal use of menthol is for this local effect. It is rubbed on the skin for headache and neuralgia, which it sometimes relieves.

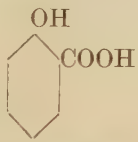
XVII

CENTRAL ANTIPYRETICS AND ANALGESICS

Phenol, as well as many of its allies previously considered, lowers the temperature of the body if given in large doses. Some of them, e.g. phenol and creosote, have been used medicinally for this purpose, but have been found too dangerous for general use as antipyretics. In 1875 it was discovered that salicylic acid lowers the temperature in some fevers. Before that time the chief antipyretic known was Quinine. Quinine, as will be seen presently, has some antipyretic action under any conditions, but a very marked action in malaria. In this disease, however, the reduction in temperature is mainly due to destruction by quinine of the causal organism of the disease, and the improvement or cure of the condition is due to the destruction of the parasite and not to the lowering of the temperature. This association of an antipyretic and curative action in quinine is accidental. When the antipyretic action of the coal-tar derivatives was discovered, it was hoped that they might also prove curative in fevers such as influenza, pneumonia, &c. So far this hope has not been realized. The antipyretics to be discussed in this chapter do not usually, so far as is known, kill off the organisms which are provocative agents of fever. While experience has shown that there is no sound reason for routine interference with a moderate pyrexia, yet often the mere reduction of fever may diminish the discomfort of the patient and tend to produce sleep. Moreover, it has been found that nearly all the antipyretics have also an analgesic action; they relieve pain by an action on the central

nervous system. While, therefore, antipyretics as a class are not definitely curative agents, they have important uses (1) for the reduction of fever which is so high as to be, *per se*, dangerous, (2) for the reduction of moderate pyrexia in certain conditions, and (3) for the relief of certain kinds of pain.

Salicylic Acid



differs from phenol in having a carboxyl group in the orthoposition, which renders it much less toxic than phenol. Salicylic acid forms fine colourless needle-shaped crystals, soluble only about 1 in 500 of water. Sodium salicylate is freely soluble in water.

Salicylic acid is an irritant to all tissues, and causes some pain and irritation of the stomach when swallowed. It has a nauseous sweet taste. It is a good antiseptic and is chiefly used in skin diseases, e.g. in the form of the *Unguentum Acidi Salicylici* (2 per cent.). Salts like sodium salicylate have a much feebler antiseptic action.

It is absorbed rapidly from the intestine, and circulates in the blood in the form of sodium salicylate. The actions of salicylic acid and of sodium salicylate after absorption are therefore identical. Salicylic acid and its salts are important chiefly from their specific action in rheumatic fever. In this fever salicylates lower the temperature, and also relieve the pain of the inflammatory joint lesions. The antipyretic action of salicylates resembles that of the more regular antipyretics of the phenacetin group, that is to say it is an action on the heat-regulating centre, increasing

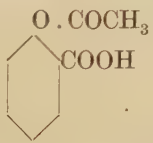
heat-loss by dilatation of the skin blood-vessels and by profuse sweating. It is difficult to explain the beneficial action of salicylates in rheumatic fever solely by this antipyretic and analgesic action, because no other antipyretics or analgesics have an equally potent effect in this particular disease, and conversely salicylates are not equally antipyretic in fevers other than acute rheumatism. It would seem justifiable, therefore, to infer that salicylates have some influence upon the causal organisms of the disease. But if this be the case, it cannot be a very powerful action, because the duration of the disease is not materially shortened nor is the danger of the spread of the infection, e.g. to the valves of the heart, markedly lessened by salicylate treatment. In this treatment of rheumatic fever dosage is important. Relatively large initial doses are required to relieve the pain and fever, after which the continuance of this relief can be maintained by smaller doses. These may have to be continued for weeks before the fever permanently subsides; otherwise the symptoms may recur when salicylates are discontinued. A common practice is to begin with a dose of 60 grains, followed by 20 grains every two or three hours until the pain or fever is subdued, after which the dose may be lessened, e.g. to 60 grains in 24 hours. The effect is of course due to the salicyl ion in the blood, and it is from that point of view immaterial whether it be given in the form of salicylic acid or of sodium salicylate. *Sodium salicylate* is preferable, however, (1) because it is far less irritant to the stomach and (2) because it is more easily prescribed owing to its easy solubility. The hydrochloric acid of the stomach will free the salicylic acid from sodium salicylate, and to check this, as well as for other reasons, it is usual to prescribe with it an alkaline salt, like sodium bicarbonate. Ordinary doses of

salicylates have usually no important effects beyond those described, but large doses in all people, and ordinary doses in people who are specially susceptible to their action, produce characteristic symptoms, of which the chief are headache, nausea, vomiting, tinnitus, deafness, and vertigo, and sometimes skin rashes and albuminuria. These symptoms of 'salicism', as it is called, come on regularly after 9 doses of 20 grains each, given at hourly intervals. They have at any rate a superficial resemblance to the symptoms of Cinchonism.

Other salicyl compounds have been introduced into medicinal use, of which the following may be mentioned.

Methyl Salicylate, Oil of Gaultheria or oil of wintergreen, is a colourless liquid, chiefly used for local application to the skin over rheumatoid painful areas like lumbago.

Acetyl Salicylic Acid or Aspirin



5–15 grains, is a white powder sparingly soluble in water, almost tasteless, and less irritating to the stomach than salicylic acid. Part of it is split up in the intestine into acetic and salicylic acids, but some of it is absorbed as the unchanged molecule. While generally its actions after absorption are similar to those of sodium salicylate, the fraction that is absorbed unchanged alters the action, especially in two ways. In the first place, aspirin is a more general analgesic than sodium salicylate, and is now very commonly used to relieve headaches and the pains of non-arti-

cular rheumatism. In the second place, the toxic symptoms produced by it are rather different. It is rare for therapeutic doses of it to induce untoward symptoms, but in a few persons it produces faintness and cyanosis and oedema of the face.

Salol (5–15 gr.), a compound of phenol and salicylic acid, is an insoluble white powder which passes unchanged through the stomach, but is hydrolysed in the small intestine into salicylic and carbolic acids. It has been used as an intestinal antiseptic, but, partly on account of its ready absorption, is of little value for this purpose.

Benzoic acid,

owing to the absence of a hydroxyl group, is physiologically less active than salicylic acid, but resembles it quantitatively. It has a feeble action in acute rheumatism. It is a less powerful antiseptic than salicylic acid and is chiefly important from its use to prevent or delay bacterial decomposition in preserved foods or beverages. Benzoinum, an oleo-resin obtained from *Styrax benzoinum*, contains benzoic acid and has been used as an antiseptic. *Tinctura Benzoini Composita* ('Friar's Balsam') (1–2 fl. dr.) is used in expectorant mixtures to diminish the viscidity of bronchial mucus, and has also been used as an antiseptic for boils, abrasions, &c. Balsam of Tolu and Balsam of Peru resemble it, but contain cinnamic as well as benzoic acid. Benzoic acid is excreted in the urine in combination with glycine forming hippuric acid, the synthesis taking place in the kidney. It was believed that a corresponding synthesis occurred also with salicylic acid, but this does not appear to occur, at any rate in man.

Derivatives of Aniline: Antipyretics of the Phenacetin Group

While antipyretic and analgesic actions, obscurely present in phenol, are conspicuous in salicylic acid and its near relatives, these actions are even more pronounced in certain derivatives of aniline. **Aniline**

has some antipyretic action, but produces dangerous collapse and destruction of red blood-cells. It is oxidized in the body to paramidophenol. By the entrance of an acetyl group into the molecule, the aniline is rendered less toxic and more resistant to oxidation. The resulting substance, **acetanilide** (1–3 gr.), has been used as an antipyretic and analgesic. It has largely been replaced by **Phenacetin** (5–10 gr.) in which an ethoxyl group has been introduced into acetanilide

It is now believed that the antipyretic action both of acetanilide and of phenacetin is due to the formation in the body of paramido phenol.

If this substance is formed rapidly, temperature falls too quickly and rises again too soon, and also toxic actions are more likely to occur, because the concentration of paramidophenol in the blood is higher for a time. With phenacetin the formation of paramidophenol occurs more slowly than with acetanilide and its effects are correspondingly less drastic and less transient. Phenacetin has been used in numberless cases both as an antipyretic and as an analgesic, and, with medicinal doses of it, toxic effects are almost unknown. With acetanilide, on the other hand, collapse symptoms are not uncommon after single large doses, and in chronic poisoning (e.g. from continued use of 'headache powders' containing acetanilide) the blood may contain a considerable proportion of methaemoglobin with a corresponding diminution in its oxidizing power.

Numerous derivatives of aniline have been investigated and many of them found to have antipyretic and analgesic actions like phenacetin, but none of them are superior to it in safety and efficiency. Its only serious rival has been **Phenazonum** (antipyrine), a more elaborate derivative of aniline, which acts much in the same way as phenacetin, but the fate of which in the body is somewhat different. Antipyrine (5–15 gr.) is freely soluble in water, whereas phenacetin is only slightly soluble (about 1 in 2,000). There is a well-marked idiosyncrasy to antipyrine, for a small proportion of people exhibit toxic symptoms when they take even small medicinal doses of it; the commoner symptoms being sweating, collapse, rapid fall of temperature, and cyanosis. Fatal effects from it are, however, rare.

Method of Action of Antipyretics. The heat-regulating centre in the brain maintains the body temperature constant within fine limits by balancing heat-loss against heat-production. But this balance is often

upset in disease, especially by the action of bacterial toxins. These usually raise the body temperature to a level which is characteristic for the particular toxin producing the fever. The antipyretics which we have previously considered, and of which the most important are salicylic acid, aspirin, phenacetin, and antipyrine, all lower a febrile temperature by increasing heat-loss, through dilatation of the skin-vessels and increased sweating. Those effects are not due to a peripheral action of those substances upon the vessels and sweat-glands, but to an action on the heat-regulating centre itself. In a fever the temperature may rise to a certain level, e.g. 103° F., and remain at this maximum while the fever lasts. The heat-regulating centre is still operative, but, under the influence of the toxin, can only maintain the temperature at this higher level. The condition has often been compared to the setting of a thermostat to a higher level. The foregoing antipyretics 'set' the centre so that it maintains the temperature at a normal, or at least lower, level. The antipyretic action is therefore due to a selective depressant action upon the nerve-cells of the heat-regulating mechanism. It is not, so far as is known, due to a destructive action upon the bacteria causing the fever or to any neutralizing action upon their toxins.

These antipyretics have a second action. They are also *analgesics*. They relieve pain by a depressant action on the pain centre, and are widely used for the relief of headache.

They relieve pain somewhat in the same way as morphine though not so powerfully, but are for various reasons much safer than morphine. They are to be preferred to it whenever possible, but there are some cases of pain which nothing but the opium alkaloids will adequately relieve.

Antipyretics of the foregoing phenacetin group are often called 'artificial antipyretics' because they are manufactured synthetically, and in contradistinction, for example, to quinine which is a natural alkaloid. Quinine not only differs in structure from the members of the phenacetin group but also offers a striking contrast to the method of action of the artificial antipyretics. For whereas these lower a febrile temperature by increasing heat-loss through their action on the heat-regulating mechanism in the central nervous system, quinine lowers the temperature (1) by diminishing heat-formation through an action on the tissue-cells, and (2)—in malaria—by a destructive action on the pathogenic organisms that provoke the fever. Seeing that the latter effect is by far the more important, quinine can be more appropriately considered later. Attention is merely drawn here to the existence of this other type of antipyretic (*v.* p. 202).

XVIII

DRUGS USED IN BACTERIAL INFECTIONS: ANTISEPTICS

In previous chapters drugs have been considered primarily from the standpoint of their actions on various organs in man, and with a view to explaining the remedial effects that they can produce in disease. A great many diseases are due to parasitic organisms, and many examples have already been incidentally given of drugs which exert, among other actions, a destructive effect on pathogenic organisms. For example, phenol, mercury, and arsenic, all have important therapeutic uses dependent upon some parasiticidal action, but, for reasons of convenience, their general actions have been discussed elsewhere. We may now consider drugs rather from the point of view of their actions upon parasites themselves, classifying them according to the type of infection for which they are chiefly used.

It will be readily intelligible that the problem of treating infective diseases will depend not only on the type of micro-organism but on the site of the infection. A particular bacterium may infect the skin, the larynx, the lungs, or the peritoneum, and the same chemical agent may not be equally applicable to each of these situations. It will be possible here only to give a brief résumé of the more important drugs which are used in the treatment of infections, and to give some indication of the type of infections for which they are chiefly used.

The deliberate use of chemical agents for destroying pathogenic micro-organisms began with Lister, who first recorded his observations in 1867. He was primarily concerned with the prevention of suppuration,

putrefaction, or 'sepsis' in wounds, and chemical agents such as phenol, which were employed to prevent such suppuration, were called antiseptics. When the work of Pasteur, Koch, and their successors showed that a very large number of diseases are due to infection by different micro-organisms, the use of chemical agents to control such infections was extended far beyond their first use to control suppuration in wounds. Though the word antiseptic is still used in its original sense of a substance which will diminish sepsis, it may now be more generally defined as a drug which inhibits the growth of micro-organisms. If the latter are actually killed, the drug is called a disinfectant.

Pathogenic organisms can be divided into a few broad classes. To a certain extent treatment of infections of each of these groups involves different problems and is often subserved by different groups of remedies.

Bacteria, which include bacilli and cocci, are minute unicellular organisms which are generally regarded as belonging to the vegetable kingdom. They give rise not only to superficial and localized infections of the skin, wounds, and mucous membranes, &c., but also to deep infections, e.g. of the lungs, peritoneum, or even of the blood itself. In some of these cases it is comparatively easy to control infection by the aid of antiseptics, in other cases it may be difficult or impossible. Some bacteria are much more easily killed than others, and spore forms are as a rule unusually resistant.

The antiseptic action of a drug can be tested by determining what concentration of it is necessary to arrest the growth of bacteria in a culture medium. So tested, a very large number of substances could be labelled as antiseptics, but only a very few of these are of any practical value in the treatment of infections.

A micro-organism is killed by some chemical interaction between it and the antiseptic, but the same interaction will be liable to take place between the antiseptic and other cells which more or less resemble the micro-organism in composition. The practical problem is, therefore, to find an antiseptic which will check the growth of bacteria without seriously damaging the cells of the tissues. This problem would probably be in most cases insoluble, were it not for the natural defensive mechanisms of the body against bacterial invasion. These are in continual operation and are, in the aggregate, of far greater value than any antiseptic. In spite of the omnipresence of pathogenic bacteria, many wounds healed spontaneously before antiseptics were introduced, and they do so now. Clearly, therefore, it is of the utmost importance not to interfere with the local or general defensive mechanisms of the body. The broad principle underlying the employment of antiseptics is to assist these mechanisms in the battle against bacterial invasion. It follows that it is not necessary that the antiseptic should kill the bacteria. If the vitality of bacteria is diminished below a certain point, the natural defensive reactions of the body, e.g. phagocytosis or antitoxin formation, are fortunately as a rule adequate to repel the bacterial invasion. It is chiefly owing to this co-operation that, especially in superficial infections of wounds or mucous membranes, a concentration of an antiseptic which will not seriously injure the tissues themselves may be effective in inhibiting the multiplication of bacteria. On the other hand, when the bacteria are of high virulence or difficult to kill or when they invade inaccessible regions or vital organs, all the means at present at our disposal may be inadequate to protect life.

An important distinction must be drawn between

local (or superficial) and remote (or general) antiseptics. If an antiseptic can reach an organ, e.g. the lungs or kidney, only by being carried to it by the blood-stream, or if the infection involve the blood itself, then all the organs of the body will be subjected to the action of the antiseptic. This will not happen to the same extent if the antiseptic be applied to a surface such as the skin or conjunctiva, or at all if the antiseptic be not absorbed from that surface. It is often true, therefore, that an antiseptic can be used for direct or local application to a surface which will be inadmissible as a remote antiseptic. Yet other disinfectants may be used for disinfecting rooms, clothing, or surgical instruments, for here no question of general or local toxic action of the antiseptic on the tissues need arise.

Superficial Antiseptics

So far as superficial infections are concerned, the same type of antiseptic may be applicable, for example, to a wound, a mucous membrane, or the skin, though even here certain antiseptics are more suitable for one region than for another.

Of antiseptics generally used for surface application which have previously been considered may be mentioned ethyl alcohol, the phenol group, and the heavy metals. Some other antiseptics can conveniently be dealt with here.

Boric Acid, Acidum Boricum, has only a feeble disinfectant action and is generally capable merely of restraining bacterial growth. It is widely used as a dusting powder, alone or diluted. It is also used in solution as a wash for catarrh of mucous membranes, e.g. in conjunctivitis or cystitis (2–4 per cent.). *Unguentum Acidi Borici* (10 per cent.) is used as a mild skin antiseptic.

Chlorine is the active antiseptic in a variety of preparations. It acts as an antiseptic by uniting with the proteins of bacteria; but as it combines also with proteins of the tissues, it tends to be rapidly used up, so that the antiseptic action is transient.

Chlorine is commonly employed in the form of hypochlorous acid or a hypochlorite which readily give off chlorine. *Eusol*, which is widely used as an antiseptic, is a solution of hypochlorous acid (about 0·3 per cent.) obtained by the action of boric acid on chlorinated lime (bleaching powder).

Chloramine-T ($C_6H_4 . CH_3 . SO_2NNaCl$) is a compound which contains about 12 per cent. of active chlorine. It forms white, almost odourless crystals, soluble 1 in 7 in water. It is less irritating than hypochlorous acid and does not give off its chlorine so rapidly. It is used in 0·1 to 2 per cent. aqueous solution for wounds or mucous membranes.

Iodine acts as an antiseptic in much the same way as chlorine. Iodine forms dark crystals with a metallic lustre, a distinctive odour, and an acrid taste. It is feebly soluble in water, soluble in solutions of iodides or in alcohol. It is an irritant, and strong solutions, e.g. *Tinctura Iodi Fortis*, B.P., may be used for counter-irritation (*v.* p. 111). Weaker solutions, e.g. *Tinctura Iodi Mitis*, B.P., 2½ per cent., are used for their antiseptic action, for example for the skin or tonsil.

Certain oxidizing agents are used as antiseptics, the most important being peroxide of hydrogen and potassium permanganate. They act by liberating oxygen which unites with proteins of bacteria but also with tissue proteins. All the available oxygen is soon given up and the antiseptic action exhausted. **Hydrogen Peroxide** (H_2O_2) is used in the form of a 3 per cent. solution, *Liquor Hydrogenii Peroxide* (B.P.), *Liquor*

Hydrogenii Dioxidi (U.S.P.). Each volume of this solution contains ten volumes of available oxygen. It gives off this oxygen very rapidly in contact with living tissues and especially with pus or blood. In addition to its bactericidal action, hydrogen peroxide has a singular value in loosening and disintegrating and bringing to the surface pus or infective material in wounds or cavities. This it does mechanically by the effervescence of oxygen. **Potassium Permanganate**, *Potassii Permanganas*, $KMnO_4$, forms dark purple prismatic crystals, odourless, soluble in about 1 in 15 in water. It liberates oxygen too slowly to produce the mechanical effect of peroxide of hydrogen. It is used chiefly as an antiseptic for mucous membranes, especially the urethra (1 in 5,000, 1 in 10,000) or for the mouth or throat. It is occasionally used for the skin, which it colours brown.

Formaldehyde (HCOH) is an irritant gas which is used in solution or as a vapour as a disinfectant for rooms, clothing, instruments, &c.

Of those mentioned, the following must be regarded merely as a few examples of antiseptics which have been found suitable for certain localities. For sterilizing the skin prior to operations, ethyl alcohol or weak tincture of iodine is frequently employed. A great variety of antiseptics are used in skin diseases and generally applied in the form of ointments, e.g. boric acid, salicylic acid, zinc oxide, mercury compounds. For mucous membranes, which are usually sensitive, irritating antiseptics must be avoided. For the conjunctiva solutions of boric acid, zinc sulphate, or protein compounds of silver are largely used, and for the urethra solutions of potassium permanganate, silver protein, or zinc sulphate. Peroxide of hydrogen and chlorine compounds are favourite antiseptics for wounds.

Remote Antiseptics

The problem is more difficult and the choice of antiseptic more limited when the attempt is made to inhibit bacterial growth in distal organs or whenever the antiseptic has to be conveyed by the blood-stream. All the organs in the body are exposed to the action of an antiseptic in the blood, and it is difficult to find a substance which will inhibit bacterial growth in a concentration which will be innocuous, especially to the more delicate organs of the body. One or two types of infection may be mentioned in which some success has been attained.

Blood Infections

When pathogenic bacteria multiply in the blood, the condition is always grave because it probably means that the defensive mechanisms of the body against the invading organism are inadequate. Many substances have been tried, usually by intravenous injection, in septicaemia, and almost invariably with indifferent results. One substance, **Mercurochrome,** a compound of mercury and fluorescein, has been used to a considerable extent in recent years by intravenous injection in such conditions, but the reports have been conflicting.

Infections of the Urinary Passages

Infections of the urethra or of the bladder may be treated locally by antiseptic injections, but infections of the urinary passages generally, including the kidney (pyelitis), can also be treated by drugs given by mouth, which are absorbed and excreted by the kidney. Some of the volatile oils, e.g. oil of sandalwood, are excreted in the urine and act as antiseptics, especially for gonorrhoeal urethritis, but they are not very

effective. Boric acid is excreted in the urine and inhibits growth of B. Coli. The most widely used urinary antiseptic is hexamine. **Hexamine** (B.P.) or **Methenamine** (U.S.P.) (Urotropine), $(CH_2)_6N_4$, is a condensation product of ammonia and formaldehyde. By itself hexamine is not antiseptic, and produces no marked physiological actions. When given by mouth, it is excreted in the urine, and, if this is acid, is decomposed with the liberation of formaldehyde which is a powerful antiseptic. It has no such action if the urine is alkaline. It is given in doses of 5–15 grains. If the urine is not sufficiently acid, acid sodium phosphate (p. 33) has to be given as well.

The possibility of using hexamine as a remote antiseptic depends upon the fact that it is carried in the blood in the relatively inert form of hexamine but is decomposed in an acid urine to liberate a more toxic and bactericidal substance. No other organ offers to the same extent the tactical advantage resulting from a sudden change in the reaction of the medium, such as is afforded by the kidney. In the case of most distal organs the antiseptic must act on the bacterium in the form in which it exists in the blood. As has already been explained, this raises the difficulty of finding a substance which will be bactericidal without being injurious to any organ. Unfortunately to most chemical substances bacteria are at least as resistant as the tissue-cells. In spite of these difficulties, some progress has been made in the treatment of two important diseases which may now be mentioned.

Leprosy

Encouraging results have been obtained in the treatment of this disease by the use of **Chaulmoogra Oil** or of preparations of it. This is a fixed oil obtained from the seeds of an Asiatic tree, preparations made

from which have long been used, especially in China, as a remedy for leprosy. The oil used to be given by mouth, but caused so much gastric irritation that really effective doses could not be given. In recent years preparations of the active principle have been given by intramuscular injection with much better results. The active principles of the oil are hydnocarpic and chaulmoogric acids—unsaturated fatty acids which are unique in possessing a closed five-carbon ring. *Oleum Chaulmoograe* (U.S.P.), an acrid yellowish-brown liquid, is given in daily doses of 5–15 minims, or ethyl esters of the fatty acids, *Aethylis Chaulmoogras* (U.S.P.), a pale yellow liquid, is given by mouth or intramuscular injection in doses of about 15 minims. It is believed that the remarkable bactericidal action of chaulmoogra preparations in leprosy is due to the action of the unsaturated fatty acids upon the waxy envelope of the bacillus. This use therefore depends upon a selective action of the antiseptic on the bacillus.

Many antiseptics have been tried against other bacterial infections, almost invariably with disappointing results.

Tuberculosis

Naturally, many remedies have been tried for tuberculosis. Perhaps the most promising remedy that would fall to be considered here is gold. It has been used in the form of a thiosulphate of sodium and gold (*sanocrysin*) which is soluble and is given intravenously. The dosage varies with the condition and reaction, of the patient, but may be 5 rising to 15 grains at weekly intervals. Many cases of phthisis have been recorded in which at least a temporary improvement has resulted from sanocrysin injections. It is still uncertain whether these act as an antiseptic

to the bacillus or by provoking some general defensive reaction of the body.

Antitoxins

The great importance of the natural defensive reactions of the body against bacterial invasion has already been mentioned. One of these reactions consists in the formation by the tissues of 'antibodies' which are shed into the blood and body-fluids and which tend to inactivate bacteria or their toxins. When a foreign protein ('antigen') is injected into an animal it provokes the formation of an 'antibody', which is specific for that particular protein. This reaction occurs to all injected proteins and to proteins only. It does not occur when they are given by mouth, because the proteins are broken down in the alimentary canal and absorbed chiefly as amino-acids which do not provoke this reaction. The amino-acids absorbed from the food can be resynthesized into proteins natural to the animal, and antibody-formation would appear to be designed to prevent the entrance and continued existence of foreign proteins in the blood or tissues. Ordinary digestion prevents this occuring with the proteins of the food.

In ordinary life there is little opportunity of foreign proteins entering the blood or tissues in an unaltered state unless conveyed by bacteria or protozoa, so that, for our limited purpose here, antibody-formation can be regarded as of importance chiefly as being one of the most important natural mechanisms for resisting invasion of bacteria, or for neutralizing the protein-like poisons or toxins which they produce. It is perhaps the most general method by which a bacterial disease is overcome and 'immunity' to it acquired.

In a disease like diphtheria for example, the injury to the patient occurs chiefly in two ways, in the first

place from the mechanical and other effects of the bacterial growth on the upper air-passages or elsewhere, and secondly as the result of the toxins formed by the bacteria which are absorbed and are powerful poisons for the heart and nervous system. Natural cure of the disease results largely from the formation of antibodies which inhibit bacterial multiplication or neutralize their toxins. If the bacterial infection be severe or if the patient have a low resistance to it, this antibody-formation will not take place to a sufficient degree or sufficiently rapidly to save the patient from the effects of the toxin. Once the toxin has combined with the heart or nervous system, antitoxin is then incapable of dislodging or neutralizing it. It would clearly be of advantage, therefore, if the patient could be supplied with the necessary antitoxin, especially before the toxin has had time to exert its injurious effects. This can be done by injecting antitoxin obtained from a horse which has been immunized to diphtheria toxin.

The procedure adopted is briefly as follows. Diphtheria toxin is first obtained from the filtrate of a broth culture of diphtheria bacillus. A horse is immunized by repeated injections (at four-day intervals) of the toxin, the dose being gradually increased according to the amount of reaction. Injections are given from four to six months until the blood acquires a sufficiently high antitoxic power. The horse is then bled to the amount of perhaps 10 litres, and the separated serum collected. The serum may be used as such or the globulins, which contain practically all the antitoxin, can be separated by fractional precipitation from the other serum proteins and used in saline solution. This antitoxic serum must be standardized according to its power of neutralizing diphtheria toxin, and this power is expressed in terms of 'units' com-

pared with a standard antitoxin. The U.S.P. directs that diphtheria antitoxin, *Antitoxinum Diphtheriticum*, should have a potency of not less than 350 antitoxin units per c.c.

Diphtheria antitoxin is of great value both as a prophylactic and curative agent against diphtheria. Its value depends largely upon its being given early and in adequate doses. The protective dose may be 1,000 units, the curative dose 10,000 units, given by injection.

Tetanus antitoxin, *Antitoxinum Tetanicum*, is prepared in a similar way from the serum of a horse immunized to tetanus toxin. It is of great value as a protective against tetanus, dose 1,500 units; and of some, though much less, value when tetanus has developed, dose 10,000 units.

These are the most important serums which are used to neutralize toxins. Sera can also be obtained to combat bacteria themselves, in which case a horse is immunized against the particular bacterium and the serum used much in the same way as antitoxic serum. Antidysenteric serum and antimeningococcic serum, for example, have been used with considerable success.

Antibacterial sera are nature's own antiseptics, and are in most cases more efficient than any artificial antiseptic. As already mentioned, they are specific for the corresponding bacterium only and have little or no influence on other micro-organisms; whereas artificial antiseptics, e.g. phenol or chlorine, the effect of which depends upon a chemical action which is more or less general for protoplasm, have a wider range of activity but a more limited efficacy. No artificial agent is known at all comparable to an antitoxin, i.e. which can neutralize a toxin once it has entered the blood-stream.

XIX

DRUGS USED IN TRYPANOSOMIASIS AND PROTOZOAL INFECTIONS

Organisms of this type, which are responsible for many widespread and important diseases, seem to belong to the animal kingdom, and it may be partly owing to this fact that they have proved, so far as present knowledge goes, more susceptible to the action of chemical agents than the bacteria, which are usually regarded as belonging to the vegetable kingdom. At any rate they seem to be more easily killed than are bacteria by concentrations of drugs which are permissible in the blood.

Trypanosomiasis

Drugs which are used in the treatment of syphilis and trypanosomiasis have already been considered. They include mercury (p. 56), bismuth (p. 65), arsenic (p. 71), antimony (p. 66), certain dyes, and 'Bayer 205' (p. 73). As has already been pointed out, a remedy which is successful for a disease due to a particular trypanosome will probably, though not necessarily, be efficacious against other trypanosomes or against spirochaetes because these organisms are closely allied. But these remedies are usually of little or no value against diseases due to protozoa of the amoeboid type which are more distantly related to trypanosomes. Of diseases due to amoeboid organisms, two require specific mention, not only because of the importance of the diseases themselves but from the successful curative results that have been achieved in them by the use of chemical remedies.

Malaria

The most efficacious remedy for malarial diseases is quinine or other alkaloids of the cinchona group.

Quinine.

Quinine is found in the bark of various species of Cinchona, which are natives of South America but are now cultivated also in the East. Cinchona bark was introduced into European medicine in the middle of the seventeenth century, and its name was derived from the Countess of Cinchon who was successfully treated by it in the earliest years of its use. Quinine was isolated from the bark in 1820, since when the use of the pure alkaloid has gradually replaced that of preparations of the crude bark. Cinchona bark contains a large number of alkaloids, about one-half of the total being quinine. Generally the other alkaloids resemble quinine in constitution and action, but none of them equal it in importance. Quinine has a complicated structural formula which is believed to include a quinoline

and a piperidine group.

Quinine differs from most other alkaloids in having no high degree of selective action. It kills all living cells in sufficient concentration. For this reason it is sometimes called a general protoplasmic poison, though it is not equally toxic to all cells. It is an antiseptic, but relatively less efficacious against bacteria than against protozoa like the malarial parasite. One of the distinguishing features of the action of quinine

is the relatively low concentrations of it that diminish the activity and vitality of protozoal organisms. It is owing to this property that it acts so successfully in malaria. The malarial parasite, when it gains entrance into the human body by the bite of an infected mosquito, reproduces itself asexually in the blood. The spores enter the red blood-corpuscles and therein undergo a series of changes, forming numerous spores which eventually burst the corpuscle and escape into the plasma. The spores later enter new corpuscles and repeat the process. According to the type of malarial parasite, this cycle occupies either two or three days, and, as the fever coincides with the liberation of the spores, there is a steep rise of temperature every two or three days, in tertian or quartan malaria respectively. Quinine destroys the parasite and therefore the fever disappears. Some types of malaria are more favourably influenced by quinine than others. If all the parasites are killed, the malaria is cured; but often, though the parasites disappear from the peripheral blood, they may persist elsewhere in the body in more resistant forms and after a variable period there may be a relapse of malaria, especially if the administration of quinine be discontinued. A common dosage in malaria is 30 grains of quinine a day for a few days, afterwards reduced to 10 grains a day.

Quinine is much less effective as an antipyretic in fevers other than malaria, and in these its action has not satisfactorily been explained. Quinine not only interferes with the vitality of living organisms but also hinders the action of unorganized ferments, e.g. the oxidizing ferments of the blood. Possibly as the result of this action it seems to diminish the metabolism of cells generally. In mammals it diminishes nitrogenous excretion and protein metabolism, with-

out, however, altering gaseous exchange. Calorimetric experiments show that it does not increase heat-loss. It acts as an antipyretic by diminishing heat-formation. In most of these fevers, however, it is not so efficient an antipyretic as the members of the phenacetin group.

Of the other pharmacological actions of quinine, that on muscle must be mentioned. Strong concentrations of quinine cause rigor of voluntary muscle. Low concentrations, such as occur in the blood after medicinal doses, may cause increased contraction of involuntary muscle, especially of the spleen or uterus. It is indeed used to promote uterine contractions in labour, but it is not comparable in power to pituitary or ergot.

Large doses, or continued maximal therapeutic doses, produce disturbances of the senses of hearing and sight; ringing in the ears, deafness, vertigo, and contraction of the field of vision (*Cinchonism*). Usually these effects are transient and disappear when the quinine is discontinued. Fatal cases of poisoning are very rare when quinine is given by mouth. Intravenously, it must be given with care (well diluted and slowly injected), otherwise it may cause respiratory and cardiac failure.

There is very marked idiosyncrasy to quinine, for some few people suffer from disorders of hearing and sight as the result of much smaller doses than produce these in the great majority of people. In others, fortunately a very few, skin rashes are produced, of which urticaria is the most troublesome.

Preparations of Cinchona Bark and Quinine. Cinchona bark contains a large number of alkaloids, of which quinine, quinidine, cinchonine, and cinchonidine are best known. These resemble one another in constitution and actions and all have some action in

malaria, but none of the alkaloids has proved superior to quinine in the treatment of this disease. Preparations of the bark, e.g. *Tinctura Cinchonae* ($\frac{1}{2}$–1 fl. dr.), may be used. but have now largely been replaced by quinine itself. Several salts of the alkaloid are in use. *Quininae Sulphas* forms light feathery crystals, with intensely bitter taste, soluble 1 in 800 in water. It can be dissolved by addition of an acid, and dilute sulphuric acid is often used for this purpose in mixtures. *Quininae Tannas* and *Quininae Aethylcarbonas* are only slightly soluble in water and practically tasteless. *Quininae Hydrochloridum* (1 in 36) or especially *Quininae Hydrochloridum Acidum* (1 in 1) can be used when a more soluble salt is necessary.

Quinidine, a dextro-rotatory isomer of quinine, has much the same action and activity in malaria as quinine itself. It is used, however, chiefly in the treatment of auricular fibrillation. It was noticed that, in patients who suffered both from malaria and auricular fibrillation, quinine sometimes stopped the fibrillation of the auricle. Quinidine was found more effective for this purpose. It does not act in the same way as digitalis (p. 154), but by prolonging the refractory period of the auricular muscle. In many cases quinidine restores the normal rhythm, whereas digitalis usually slows the ventricular rate without abolishing the fibrillation of the auricle. The sudden restoration of normal auricular beats by quinidine may dislodge a clot from the auricle and, when the possibility of this occurrence is suspected, digitalis is safer. Quinidine must therefore be given with caution. Usually a preliminary dose of 3 grains is given to see whether the patient is not unduly sensitive to it, but the usual effective dosage is 3–6 grains three times a day for one to three days.

Amoebic Dysentery

This disease is, like malaria, due to an amoeboid organism, which is, however, probably not very closely related to the malarial organism. In any case quinine has but little effect on amoebic dysentery, and conversely ipecacuanha, the actions of which may here be considered, has little or no beneficial action in malaria.

Ipecacuanha.

Ipecacuanha is the dried root of *Psychotria Ipecacuanha* (B.P.) or *Cephaelis Ipecacuanha* (U.S.P.), a small shrub which grows in Brazil. It began to be imported into Europe in the seventeenth century as a remedy for dysentery. For this it has been used more or less continuously since, at first with varying success but with more certain results in recent years since it has been realized that it is only in one particular form of dysentery—that due to amoebic infection—that it has a curative action. In the course of time it has acquired other therapeutic uses.

The active principles of ipecacuanha root are alkaloids, of which the most important is emetine. Emetine has a peculiar irritant action which it can display even on the skin, but more conspicuously on mucous membranes. The first group of actions to be described are the result of this irritant action. Thus when taken by mouth in doses of about 15 grains of the powdered root, it produces vomiting reflexly through irritation of the mucous membranes of the stomach. Vomiting is slow in onset and accompanied by much nausea, and is apt to be repeated. Where speedy emesis is desirable, e.g. in cases of poisoning, ipecacuanha is therefore unsuitable.

It is more often used for effects which accompany

gastric irritation, namely increased bronchial and sweat secretion. Increased bronchial secretion is a natural protective reaction to facilitate removal of foreign bodies which irritate air-passages. This secretion is normally excited by irritation of afferent fibres in the mucous membrane of the trachea and bronchi, but stimulation of the afferent vagal fibres of the mucous membrane of the stomach can also excite the centre for bronchial secretion. The degree of irritation necessary to produce this effect is something short of that necessary to evoke vomiting. Hence doses of ipecacuanha, e.g. about 1 grain, too small to produce vomiting, can cause increased secretion from the bronchial mucous membrane. This effect can be produced similarly by other gastric irritants, e.g. tartar emetic, ammonium carbonate, squill, &c. Many such substances can therefore be used as expectorants. Preparations of ipecacuanha commonly used for this purpose are *Vinum Ipecacuanhae* (B.P.) in doses of 10–30 minims or *Syrupus Ipecacuanhae* (U.S.P.) in doses of 15 minims. To produce vomiting with these preparations, about ten times as much must be given.

A second accompaniment of gastric irritation is increased sweating. This is produced reflexly in much the same way as increased bronchial secretion, and indeed a cold sweat is a well-known concomitant of nausea from any cause.

A famous powder used for this purpose is *Pulvis Ipecacuanhae Compositus* (B.P.) or *Pulvis Ipecacuanhae et Opii* (U.S.P.) or Dover's Powder. The originator of this powder, Thomas Dover, was a romantic figure. If he had not turned buccaneer for a few years, the story of Robinson Crusoe would never have been written, for it was Captain Thomas Dover on the privateer *Duke* who rescued Alexander Selkirk in 1709 after he had lived alone on an island for over four years, and

whose story Defoe later wrote. Returning with a ship full of treasure in 1710, Dover at the age of forty began the practice of medicine with no qualifications other than that he had been at one time a servant of Sydenham. Perhaps his chief legacy to medicine was the powder which still bears his name. This powder, as now compounded, contains 10 per cent. each of ipecacuanha and opium, potassium sulphate making up the bulk of the powder. It is an efficient diaphoretic, ipecacuanha increasing the secretion of sweat—an effect which is enhanced by the dilatation of the skin-vessels produced by opium. The dose is 5–15 grains. Dover's powder has to some extent been supplanted by newer diaphoretics such as aspirin.

The most important therapeutic use of ipecacuanha is in a type of dysentery, especially prevalent in tropical countries, due to infection with a particular amoeba, *Entamoeba histolytica*. This amoeba infects the intestine but may migrate from the intestinal canal and produce abcesses in the liver. The earliest use of ipecacuanha was in this disease, and it used to be given by mouth. In recent years it has been found that a more rapid and complete cure can be effected by administering the active principle **emetine**. The hydrochloride of this alkaloid is given hypodermically in a daily dose of $\frac{1}{2}$–1 grain for several days. In many cases the amoebae disappear from the stools and liver, and the symptoms of the disease disappear. If this treatment fails, emetine in the form of **emetine-bismuth iodide** (an insoluble salt which is not decomposed to liberate emetine until it reaches the intestine) is given by mouth in daily doses of 3–4 grains for about ten days. This usually cures the disease.

XX

DRUGS USED IN WORM INFECTIONS: ANTHELMINTICS

A VARIETY of diseases, some of great practical importance, especially in tropical and subtropical countries, are due to infection by worms. Here we have to deal with parasites far more highly organized, though not always more potent for ill, than the lowly protozoa or spirochaete. It will not be surprising that, for diseases due to two groups of parasites phylogenetically so remote from one another, different remedies are usually necessary.

In some cases worms inhabit the tissues of the host. This is the case, for example, with Bilharzia and Filaria. Diseases due to these have usually to be treated by intravenous injections, and the most important remedy so used is antimony, which has already been considered (p. 66).

In other cases the adult worm lives in the alimentary canal of the host, and drugs used to expel intestinal worms may be taken here. A drug used against worm infection is called an anthelmintic. If the worms are killed, it may be also called a vermicide. An anthelmintic may cause expulsion of live worms from the intestine, in which case the term vermifuge is preferable.

Different kinds of worms may be found in the intestine and, as they belong to different species, the same anthelmintic is not equally toxic to all. Frequently more than one anthelmintic is in use for any particular worm, so that it is convenient to group the anthelmintics according to the variety of worm for which each is chiefly used. It must be remembered,

however, that the vermifuges so grouped together may have little in common, chemically or pharmacologically, beyond this anthelmintic action.

The attempt to get rid of intestinal worms will usually be successful only if attention be paid to details of treatment. It is generally advisable, before giving an anthelmintic, to have the stomach and intestine fairly empty of contents, so as to ensure access of the anthelmintic to the worm, without the drug being too diluted. This can be attained by keeping the patient on a light fluid diet on the previous day and by giving a purge. After the anthelmintic has had time to produce its effect it is usual to follow it with a second purgative, in order to remove any unabsorbed part of the drug, as well as to effect evacuation of dead or paralysed worms.

Tape-worms or Cestodes (Taenia and Bothriocephalus)

Aspidium Filix Mas (Male Fern), the rhizome of a species of fern widely distributed over temperate regions, has been used for centuries as a vermifuge for tape-worm and is still the favourite drug for this purpose. The active principles are derivatives of phloroglucin and butyric acid, among them being filicic acid and filmaron. These are insoluble in water, and the preparation of male fern chiefly used is an ether extract, *Extractum Filicis Liquidum* (B.P.), or *Oleoresina Aspidii* (U.S.P.), a viscid oily-looking preparation which is administered in capsules or suspended in mucilage in an average dose of 60 minims. The active principles are highly toxic if absorbed, but owing to their insolubility, the extract does not usually cause toxic symptoms. In cases of unusual absorption or overdosage the extract may produce gastro-intestinal irritation, with vomiting, diarrhoea, and

abdominal pain, or in more severe cases convulsions or coma. Optic neuritis, leading to temporary or, rarely, permanent blindness, has occurred.

Pelletierine, an alkaloid obtained from the bark of the pomegranate, is also used as an anthelmintic for tape-worms. It is usually given in the form of *Pelletierine tannate* in doses of about 4 grains.

Round-worms or Nematodes

For infection by the common 'round-worm' (*Ascaris Lumbricoides*) the usual remedy is **Santonin**, a crystalline naphthalene derivative, obtained from the flower-heads of *Artemisia maritima*, which grows widely in the salt-marshes of Russia and elsewhere. These flowers, under the name 'worm-seed', have been used since early times for their anthelmintic action, and have now been replaced by their active principle, santonin, which was first isolated in 1830. Santonin forms colourless crystals, which turn yellow on exposure to sunlight. It is almost insoluble in water, but soluble in alkalis. The round-worms are not killed by santonin but are expelled alive. Santonin is given in the form of *Trochiscus Santonini* (B.P.), 1 grain in each, or in the form of tablets, a total of three grains being a common adult dose.

Most of the santonin passes through the alimentary canal unabsorbed, the small amount excreted in the urine giving it a yellowish colour, or pinkish if alkaline. When absorbed in considerable quantities, santonin produces characteristic effects, especially disorders of colour vision. The most usual effect is yellow vision (xanthopsia) or occasionally violet vision, the colour depending to some extent on the intensity of illumination, and the visual changes seem to be due to an interference with violet perception in the retina. Santonin may also produce nausea and vomiting and,

if absorbed in large quantities, epileptiform convulsions due to cerebral stimulation.

Thread-worms (Oxyuris)

These are small worms which usually inhabit the rectum and are relatively easily dislodged by rectal injections, e.g. of infusion of quassia or of soap and water. If these measures fail, santonin, ferric chloride, or oil of chenopodium can be given by mouth.

Hook-worms

These are small nematodes, not over half an inch long, which live in the jejunum. There are at least two varieties, *Ankylostoma duodenale* or Old World Hook-worm, and *Necator Americanus* or New World Hook-worm. In certain regions hook-worm infection is responsible for much ill health, especially a form of progressive anaemia, so that the treatment of such infection is of great practical importance. The three chief remedies are thymol, oil of chenopodium, and carbon tetrachloride.

Thymol (*v.* p. 178) is usually given in doses of 15–30 grains in cachets or capsules, sometimes repeated in 2 hours, and followed in 6–8 hours by a brisk purgative. Toxic symptoms occur occasionally, especially headache, vomiting, giddiness, tinnitus, and cardiac weakness.

Oil of Chenopodium is a crude volatile oil obtained from *Chenopodium anthelminticum*, a weed growing widely in the United States and which was used as a domestic remedy for infection by worms. The chief constituent of the oil is an oxidized terpene, Ascaridol. In adults a usual dose is 3 c.c. divided into two doses, given two hours apart and followed two hours later by a purgative dose of castor oil.

Carbon Tetrachloride, Tetrachlormethane, CCl_4,

which resembles chloroform in some ways in its action, has been used since 1921 as an efficient remedy for hook-worm. It is given in doses of 2–3 c.c. in milk or water. Nausea, vomiting, giddiness, and drowsiness may follow its use, but are less likely to occur if it is followed by a purge.

INDEX

Absinthe, 80.
Acetanilide, 185.
Acetate of Potash, 22.
Acetphenetidin (phenacetin), 185.
Acetyl salicylic acid, 183.
Acids.
  Acetyl salicylic, 183.
  Benzoic, 184.
  Boric, 192.
  Carbolic, 172.
  Citric, 31.
  Diethylbarbituric, 103.
  Hydrochloric, 31, 37.
  Hydrocyanic, 123.
  Prussic, 123.
  Salicylic, 181.
  Tannic, 45.
Aconite, 122.
Aconitine, 122.
Adrenaline, 139.
Aether, 92.
Agar, 38.
Alcohol, ethyl, 83.
Alcohol, methyl, 90.
Alkalis, 33.
  Action on stomach, 37.
  Action on urine, 34.
Almond, bitter, 125.
Aloes, 43.
Aloin, 43.
Alum, 52.
Aluminium, 52.
Amines, 142.
Ammonium carbonate, 30.
Ammonium chloride, 29.
Amygdala amara (bitter almond), 125.
Amyl nitrite, 150.
Anaesthetics (*General*), 91–9.
  Chloroform, 95.
  Ether, 92.
  Ethyl chloride, 96.
  Ethylene, 98.
  Nitrous oxide, 97.
Anaesthetics (*Local*), 115–26.
  Aconite, 122.
  Belladonna, 135.
  Cocaine, 115.
  Ethyl chloride, 97.
  Hydrocyanic acid, 123.
  Menthol, 179.
  Novocaine, 121.
  Stovaine, 121.
Analgesics (*Central*), 180–3, 185–7.
  Acetanilide, 185.
  Antipyrine, 186.
  Aspirin, 183.
  Morphine, 106.
  Phenacetin, 185.
Aniline, 185.
Anise, 177.
Anthelmintics, 209.
  Antimony, 67.
  Carbon tetrachloride, 212.
  Chenopodium, 212.
  Filix Mas, 210.
  Pelletierine, 211.
  Quassia, 212.
  Santonin, 211.
  Thymol, 212.
Anthracene purgatives, 41.
Antifebrine (acetanilid), 185.
Antimony compounds, 66.
Antipyretics, 180, 202.
  Acetanilide, 185.
  (Aconite, 123.)
  Alcohol, 85, 89.
  Antipyrine, 186.
  Aspirin, 183.
  Ipecacuanha, 207.

Phenacetin, 185.
Quinine, 203.
Sodium salicylate, 182.
Antipyrine, 186.
Antiseptics, 52, 53, 60, 189.
Alcohol, 83.
Boric acid, 192.
Chloramine-T., 193.
Chlorine, 193.
Cresols; lysol, tar, 174.
Hydrogen peroxide, 193.
Iodine, 193.
Mercury compounds, 57, 60.
Phenol, 172.
Potassium permanganate, 194.
Salicylic acid, 181.
Silver compounds, 53.
Thymol, 178.
Volatile oils, 178.
Zinc sulphate, 52.
Antitoxin, diphtheria, 198.
Antitoxin, tetanus, 200.
Apomorphine, 109.
Aquae, 15.
Arecoline, 132.
Argenti nitras, 53.
Argenti proteinum, 54.
Arsenic, arsenious acid, 68.
Arsenic, organic compounds, 70.
Arsenobenzol (Salvarsan), 71.
Arsphenamine, 71.
Artemisia, 211.
Aspidium, 210.
Aspirin, 183.
Assay, biological, 72, 158.
Astringents, 45, 49.
Alcohol, 83.
Alum, 52.
Bismuth compounds, 65.
Ferric chloride, 62.
Lead acetate, 54.
Silver nitrate, 53.
Tannin, 45.
Zinc sulphate, 52.
Atophan, 165.
Atoxyl, 71.
Atropa belladonna, 134.
Atropine, 134.

Balsams, 184.
Barbital, barbitonum, 103.
Barium, 146.
'Bayer 205', 73.
Belladonna, 134.
Benzoic acid, 184.
Benzoin, 184.
Benzol, 171.
Bicarbonate of soda, 34, 37.
Biological assay of drugs, 72, 158.
Bismuth, 65.
Bitters, 36.
Blaud's Pill, 64.
Blister, fly, 115.
Boric acid, 192.
Bromides, 104.
Bronchi, v. *Expectorants*.
—, *dilators of*.
— Adrenaline, 142.
— Atropine, 135.
— Ephedrine, 143.
— Hyoscine, 138.
— Nitrites, 152.

Caffeine, 76.
Calabar bean, 132.
Calcium carbonate, 29.
— chloride, 29.
— lactate, 29, 32.
Calomel, 58, 60.
Calumba, 36.
Camphor, 178.
Camphorated oil, 114, 178.
Cannabis indica, 110.
Cantharides, 115.
Capsicum, 177.
Carbolic acid, 172.
Carbon tetrachloride, 212.
Carbonates, 33.

Carminatives, 37, 177.
Cascara, 42.
Castor oil, 39.
Catechu, 47.
Cathartics, v. *Purgatives*.
Caustics, 31, 33, 50.
Charcoal, 38.
Chaulmoogra oil, 196.
Chemical constitution and Pharmacological action, 6.
Chenopodium oil, 212.
Chloral hydrate, 100.
Chloramines, 193.
Chlorine, 193.
Chloroform, 95.
Chrysophanic acid, 42.
Cinchona, 202.
Cinchophen, 165.
Cinnamon, 177.
Citrates, 34.
Citric acid, 31.
Cocaine, 115.
Codeine, 108.
Cod-liver oil, 168.
Colchicum, 166.
Colocynth, 41.
Congenital tolerance for drugs, 10.
Copaiba, 178.
Copper sulphate, 50.
Counter-irritants, 111.
  Camphor, 178.
  Cantharides, 115.
  Capsicum, 177.
  Mustard, 114.
  Turpentine, 114.
Corrosive sublimate, 57.
Creosols, 174.
Creosote, 174.
Creta, 29.
Croton oil, 40.
Cubebs, 178.
Cumulative poisoning, 55, 157.
Cupri sulphas, 50.
Curare, 125.
Diacetyl morphine, 109.
Diamorphine, 109.
Diaphoretics.
  Ipecacuanha, 207.
  Pilocarpine, 131.
  Sodium salicylate, 182.
  Tartar emetic, 66.
Diethylbarbituric acid, 103.
Digitalis, 154.
Digitoxin, 157.
Dill, 178.
Dimethylxanthine, 79.
Diphtheria antitoxin, 199.
Diuretics.
  Caffeine, 78.
  Digitalis, 156.
  Diuretin, 79.
  Mercury, 58.
  Novasurol, 61.
  Salts, 21, 22.
  Squills, 160.
  Theobromine, 79.
  Urea, 22.
Dover's powder, 207.

Elaterium, 41.
Emetics.
  Ammonium carbonate, 30.
  Apomorphine, 110.
  Copper sulphate, 51.
  Ipecacuanha, 206.
  Mustard, 114.
  Sodium chloride, 21.
  Tartar emetic, 66.
  Zinc sulphate, 52.
Emetine, 206, 208.
Emetine bismuth iodide, 208.
Emplastra, 16.
Enemata, 16, 44.
Ephedrine, 143.
Epinephrine, 139.
Epsom salts (magnesium sulphate), 23.
Ergamine, 148.
Ergot, 144.

Ergotamine, 143.
Ergotoxine, 143.
Erythrol tetranitrate, 152.
Eserine (Physostigmine), 125, 132.
Essential oils, 175.
Ether, 92.
Ethyl alcohol, 83.
Ethyl chloride, 96.
Ethylene, 98.
β-Eucaine, 121.
Eucalyptus oil, 178.
Eusol, 193.
Expectorants.
Ammonium carbonate, 30.
Apomorphine, 110.
Iodides, 164.
Ipecacuanha, 207.
Squills, 160.
Tartar emetic, 66.

Ferrous and ferric compounds, 62.
Filix mas, 210.
Flavouring agents, 177.
Formaldehyde, 194.
Fowler's solution, 70.
Foxglove, 154.
Friar's balsam, 184.

Galls, 45.
Gamboge, 41.
Gaultheria oil, 183.
General anaesthetics, v. *Anaesthetics.*
Genito-urinary antiseptics, 178, 195.
Gentian, 37.
Germanin, 73.
Gin, 178.
Glycerine, 45, 15.
Gold, 197.
Gregory's powder, 44.
Grey powder, 60.
Guaiacol, 174.
Gum saline, 26.

Hamamelis, 47.
Heart—Stimulants.
Adrenaline, 141.
Alcohol, 88.
Ammonia, 30.
Atropine, 135.
Camphor, 179.
Tyramine, 143.
Tonics.
Digitalis, 154.
Strophanthus, 158.
Sedatives (auricular fibrillation.)
Digitalis, 155.
Quinidine, 205.
Heroine, 109.
Hexamine, 196.
Hippuric acid, 184.
Histamine, 148.
Homatropine, 137.
Hydrargyrum (mercury), 56.
Hydrates, 33.
Hydrochloric acid, 33, 37.
Hydrocyanic acid, 123.
Hydrogen peroxide, 193.
Hyoscine, 138.
Hyoscyamine, 135, 138.
Hyoscyamus, 138.
Hypertonic solutions, 21, 23.
Hypnotics.
Alcohol, 89.
Bromides, 104.
Cannabis, 110.
Chloral hydrate, 100.
Heroine, 109.
Luminal, 104.
Morphine, 106.
Paraldehyde, 102.
Sulphonal, 102.
Trional, 103.
Veronal, 103.
Hypochlorites, 193.
Hypodermic injections, 12, 19.

Idiosyncrasy, 10.
Infusa, 15.
Inhalation of drugs, 92, 150.
Injection of drugs, 12.
Insulin, 168.
Iodides, 163.
Iodine, 163, 193.
Ipecacuanha, 206.
Iron, 62.
Irritants, v. *Counter-irritants.*

Jaborandi, 131.
Jalap, 41.
Juniper, oil of, 178.

Kino, 47.
Krameria, 47.

Lamellae, 16.
Laxatives, v. *Purgatives.*
Lead, 54.
Lemon juice, 167.
Lime salts, 29.
Liniments, 16.
Liquorice powder, 42.
Liver, 70.
Local anaesthetics, v. *Anaesthetics.*
Lozenges, 15.
Luminal, 104.
Lysol, 174.

Magnesia, 34.
Magnesium sulphate, 23.
Menthol, 179.
Mercurochrome, 195.
Mercury, 56.
Metals, heavy, 48.
Methyl alcohol, 90.
Methyl salicylate, 183.
Misturae, 15.
Mixtures, 15.
Morphine, 106.
Muscarine, 132.
Mustard, 114.

Narcotics, v. *Hypnotics.*
Narcotine, 108.
Neoarsphenamine, 73.
Neosalvarsan, 73.
Nicotine, 130.
Nitrates, 22.
Nitrites, 150.
Nitroglycerine, 152.
Nitrous ether, 152.
Nitrous oxide, 97.
Novasurol, 61.
Novocaine, 121.

Oils, fixed, 39, 168.
Oils, volatile or essential, 175.
Opium, 105, 109.
Oxidising disinfectants, 193, 194.

Papaverine, 108.
Paraffin, liquid, 38.
Paraldehyde, 102.
Paramidophenol, 186.
Parathyroid gland extract, 162.
Pelletierine, 211.
Pepper, cayenne, 177.
Peppermint, 177.
Pepsin, 37.
Permanganate of potash, 194.
Peroxide of hydrogen, 193.
Peru, balsam of, 184.
Pharmacognosy, definition of, 4.
Pharmacology, definition of, 4.
Pharmacopoeias, 4.
Pharmacy, definition of, 4.
Phenacetin, 185.
Phenazone, 186.
Phenobarbital, 104.
Phenol, 172.
Phenolphthalein, 44.
Phenylquinoline carbolic acid, 165.
Phosphate, acid sodium, 33.
Phosphate of soda, 24.
Phosphorus, 74.

Physostigmine, 125, 132.
Pilocarpine, 131.
Pills, 15.
Pilulae, 15.
Pituitary gland, 146.
Pix liquida, 174.
Plasters, 16.
Plumbi acetas, 54.
Podophyllum, 41.
Potassium.
— acetate, 22.
— bicarbonate, 34, 37.
— bromide, 104.
— citrate, 34.
— iodide, 163.
— permanganate, 194.
Protargol, 54.
Prussic acid, 123.
Pulveres, 15.
Pupil, dilators of.
Atropine, 136, 137.
Cocaine, 117.
Homatropine, 137.
Hyoscine, 138.
—, *constrictors of*:
physostigmine, 133.
pilocarpine, 131, 133.
Purgatives.
Agar, 38.
Aloes, 43.
Cascara, 42.
Castor oil, 39.
Colocynth, 41.
Enemata, 44.
Glycerine, 45.
Jalap, 41.
Liquid paraffin, 38.
Mercury, 60.
Phenolphthalein, 44.
(Physostigmine, 134.)
(Pituitary, 148.)
Podophyllum, 41.
Rhubarb, 43.
Salines, 22.
Scammony, 41.
Senna, 42.
Sulphur, 39.
Purin diuretics, 79.
Pyrogallol, 175.

Quassia, 36.
Quinidine, 205.
Quinine, 202.

Rectal administration of drugs, 16.
Regional anaesthesia, 119.
Respiratory Stimulants (*Central*).
Atropine, 136.
Caffeine, 77.
Strychnine, 82.
— *Sedatives* (*Central*).
Codeine, 108.
Heroine, 109.
Morphine, 107.
Rhatany, 47.
Rheum, 43.
Rhubarb, 43.
Ricin, 40.
Ricinus communis, 39.
Ringer's solution, 25.

Sal volatile, 30.
Salicylate of soda, 182.
Salicylic acid, 181.
Saline diuretics, 22.
Saline infusion, 19, 25, 26.
Saline purgatives, 22.
Salol, 184.
Salt action, 20.
Salvarsan, 71.
Sandalwood oil, 178.
Sanocrysin, 197.
Santonin, 211.
Scammony, 41.
Scilla, 159.
Scopolamine (Hyoscine), 138.
Seidlitz powder, 24.
Senna, 42.
Silver nitrate, 53.
protein compounds, 54.

Sinapis, 114.
Smelling salts, 30.
Sodium, chloride, 21.
— phosphate, 24.
— sulphate, 24.
Soporifics, v. *Hypnotics.*
Spanish fly, 115.
Spirits, 15.
Squills, 158.
Stibines, 67.
Stovaine, 121.
Stramonium, 138.
Strophanthin, 159.
Strophanthus, 158.
Strychnine, 80.
Sulphates, 24.
Sulphonal, 102.
Sulphur, 39, 42.
Sulphuric acid, 31, 33.
Suppositories, 16.
Suprarenal glands, 139.
Syrups, 15.

Tabellae, 15.
Tannic acid, 45.
Tar, 174.
Tartar emetic, 66.
Tartrate of soda and potash, 24.
Tea, 76.
Theobromine, 79.
Theocine, 79.
Theophylline, 79.
Thymol, 178, 212.
Thyroid gland, 161.
Thyroxine, 162.
Tinctures, 15.
Tolerance of drugs, 10.
Tolu, balsam of, 184.
Trional, 103.
Trochisci, 15.
Tryparsamide, 73.
Turpentine, 177.
Twilight sleep, 138.
Tyramine, 143.

Unguenta, 16.
Urea, 22.
Urinary Secretion, v. *Diuretics.*
increase acidity:
Acid sodium phosphate, 33.
diminish acidity:
Acetates, 34.
Bicarbonates, 34.
Citrates, 34.
Urotropine, 196.
Uterine Stimulants.
Ergotoxine, 143.
Ergot, 144.
Pituitary, 148.
Quinine, 204.
(Adrenaline, 142.)
(Histamine, 149.)
(Lead, 56.)
Vaso-constrictors.
central:
Caffeine, 77.
Strychnine, 82.
reflex:
Ammonia, 30.
Camphor, 179.
peripheral:
Adrenaline, 139.
Pituitary, 147.
Tryamine, 143.

Vaso-dilators.
Nitrites, 150.
Alcohol, 88.
Vermifuges, v. *Anthelmintics.*
Veronal, 103.
Vesicants, 115.
Vitamins, 166.
Volatile oils, 114, 175.

Water, 18.

Xanthine compounds, 79.

Young's rule of dosage, 10.

Zinc, 52.

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